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HOW SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AFFECTS IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY

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TITLE: HOW SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AFFECTS IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY.

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ABSTRACT

Objectives: Coronavirus Induced Disease 2019 (COVID-19) causes lung parenchymal and endothelial damage that cause hypoxia and hypoxic acute respiratory failure (hARF). Severity of disease has been based on indirect measurements of hypoxia. If the severity of hARF may influence patient outcomes is still unknown.

Design: observational, prospective, multicenter study.

Setting: the study was conducted in three academic hospitals in Milan (Italy) involving three intermediate respiratory care units and three general wards.

Participants: consecutive adult hospitalized patients with a virologically-confirmed diagnosis of COVID-19 were enrolled. No specific exclusion criteria were applied.

Interventions: anthropometrical, clinical characteristics and blood biomarkers were assessed within the first 24 hours from admission until the discharge or death. hARF was graded as follows: severe (partial pressure of oxygen to fraction of inspired oxygen ratio [PaO2/FiO2] <100 mmHg); moderate (PaO2/FiO2 101-200 mmHg); mild (PaO2/FiO2 201-300 mmHg) and normal (PaO2/FiO2 >300 mmHg).

Primary and secondary outcome measures: the primary outcome was the assessment of clinical characteristics and in-hospital mortality based on the severity of respiratory failure. Secondary outcomes were intubation rate and application of continuous positive airway pressure (CPAP) during hospital stay.

Results: 412 patients were enrolled (280 males, 68%). Median (interquartile range – IQR) age was 66 (55-76) years with a PaO2/FiO2 at admission of 262 (140-343) mmHg. 50.2% had a cardiovascular disease (CVD). Prevalence of mild, moderate and severe hRF was 24.4%, 21.9% and 15.5%, respectively. In-hospital mortality proportionally increased with increasing impairment of gas exchange (p-value<0.0001). The only independent risk factors for mortality were older age (Hazard rate (HR) 1.1; 95% confidence interval (CI): 1.1-1.1, p-value<0.0001) and the severity of hARF at admission (HR 0.99; 95%CI: 0.99-0.99, p-value<0.0001).

Conclusions: The PaO2/FiO2 value is independently associated with in-hospital mortality. Clinical severity of COVID-19 should be re-considered based on hARF severity.

Trial registration: NCT04307459

STRENGTHS AND LIMITATIONS (LIMITED TO METHODS)

- This was a multicentre, prospective study
- The study has enrolled a conspicuous of well characterized patients hospitalized with COVID-19 pneumonia
- A selection bias may be due to the high number of severe patients due to the Hub characteristics of the participating centres
- Not all patients were evaluated in room air conditions at admittance, thus potentially underestimating the severity of the study sample

INTRODUCTION

The severe acute respiratory syndrome Coronavirus type 2 (SARS-CoV-2) and the related coronavirus disease 2019 (COVID-19) has caused a pandemic and ~280.000 deaths.[1] The clinical spectrum can range from mild symptoms (e.g., fever and malaise) to a severe hypoxic respiratory failure, sepsis, multi-organ involvement, and death. The infection appears to induce an inflammatory reaction with pulmonary infiltrates generating hypoxemia secondary to intra-parenchymal shunt and ventilation/perfusion mismatch, favored by endothelial damage and dysfunction, and altered regulation of perfusion and associated with macro and/or micoembolism.[2,3] So far, risk factors such as older age,[4-6] severity of clinical presentation [4-7], increased D-dimer values,[4] cardiovascular disease (CVD),[4,5] and hypertension [5-8] have been associated with unfavorable outcomes.

It has been proposed that clinical severity of COVID-19 should depend on the presence of any of the following criteria: a partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio <300 mmHg, a respiratory rate >30 per minute, and a peripheral oxygen saturation (SpO2) <93%.[4, 9-12] Several consensus statements recommend different PaO2 and SpO2 thresholds to prescribe continuous positive airway pressure (CPAP),[13-15] non-invasive ventilation, or intubation.[16] It is still unknown if the severity of respiratory failure may influence patient outcomes.

The aim of the present study was to assess the clinical characteristics of COVID-19 patients based on the severity of respiratory failure, and to explore the relationship between the degree of gas exchange impairment and clinical outcomes (mechanical ventilation and mortality).

METHODS

An observational, prospective, multicenter study was conducted in three academic hospitals in Milan (Italy) from March 7 to May 7, 2020, involving three intermediate respiratory care units and three general wards. A detailed list of participating centers is reported in *Supplemental material S1*. The study protocol (ClinicalTrials.gov: NCT04307459), designed following the amended Declaration of Helsinki (2013), was approved by the local ethical committee (Comitato Etico Milano Area I; 17263/2020) and all recruited patients gave written informed consent. The authors received no specific funding for this work.

Patient and Public Involvement

No patient involved

Patients

Adult hospitalized patients with a virologically-confirmed diagnosis of SARS-CoV-2 infection or with COVID-19-related symptoms and radiological signs during the pandemic period were considered eligible for study enrolment. Patients with <18 years old or unable to provide informed consent were excluded from the study. Hospitalization criteria are reported in *Supplemental material S1*.

Procedures

Anthropometrical and clinical characteristics were collected at admission. The PaO2/FiO2 ratio was calculated from the first available arterial blood gas analysis performed in the emergency department. PaO2/FiO2 thresholds to grade severity of respiratory failure were taken from the Acute Respiratory Distress Syndrome (ARDS) Berlin definition, and were:[17] normal (PaO2/FiO2 >300 mmHg); mild (PaO2/FiO2 201-300 mmHg); moderate (PaO2/FiO2 101-200 mmHg); severe (PaO2/FiO2 ≤100 mmHg). Blood count and biochemistry parameters were assessed during the first 24 hours after hospital admission.

Outcomes

The primary outcome was the description of patients' clinical characteristics at admission and the assessment of in-hospital mortality based on the severity of respiratory failure.

Secondary outcomes were the assessment of intubation rate and application of CPAP during the hospital stay.

Study definitions

SARS-CoV-2 infection and co-infections

Nasopharyngeal swab specimens were collected in the emergency department. *SARS-CoV-2* infection was proved by means of reverse transcriptase polymerase chain reaction (RT-PCR). Co-infection with *Influenza virus* A and B, A*denovirus*, *human Rhinovirus, Respiratory Syncytial virus*,

human Metapneumovirus were also investigated and analyzed by means of RT-PCR or rapid influenza diagnostic tests (RIDTs).[18] Microbiological testing for bacteria and fungi in blood, upper and lower airway tract, sputum and urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed according to standard operating protocols.

Management of respiratory failure

Helmet CPAP was the only non invasive respiratory support used in patients with confirmed or suspected COVID-19 pneumonia not responsive to oxygen masks in order to reduce the viral exposure of the healthcare workers in rooms without negative pressure.[19] Patients with a PaO2/FiO2 ratio <300 mmHg in room air were administered oxygen with nasal cannulae to reach a SpO2 of 94% or PaO2 >60 mmHg; in case of unsuccessful intervention within 30 minutes, patients were put on reservoir masks with 90-100% FiO2 or helmet CPAP was initiated with PEEP up to 12 cmH2O based on the respiratory distress and comorbidities following standard operating procedures as previously described.[14] CPAP failure after two hours with the maximal tolerable PEEP and a FiO2 of 100% was considered in case of: a) persistence of PaO2/FiO2<300 mmHg; b) hemodynamic instability (systolic blood pressure <90 mmHg despite adequate fluid support) or altered consciousness; d) respiratory distress, fatigue and/or a respiratory rate >30 bpm.[20] Patients that fulfilled CPAP failure criteria were evaluated by an ICU physician for potential intubation. A do not intubate (DNI) order was established by the treating attending physician following a multidisciplinary discussion with the unit staff and the ICU and based on patient's age, comorbidities and clinical status.

In hospital treatment

Unless contraindicated, patients received hydroxychloroquine and lopinavir/ritonavir following local standard and Italian guidelines.[21,22] Methylprednisolone was given at a maximal dose of 1 mg/Kg in patients with severe pneumonia according to the ATS/IDSA guidelines.[23] Immunomodulation with off-label tocilizumab at a dosage of 8 mg/Kg body weight was administered in patients with signs of hyper-inflammatory syndrome and elevated IL-6.[21] Unless contraindicated, patients received prophylactic low molecular weight heparin (LMWH) or were switched to therapeutic LMWH dosage

if already on chronic anticoagulant therapy. Patients with signs of deep vein thrombosis, pulmonary embolism or D-dimer values >5,000 received a therapeutic dose of LMWH.

Statistical Analysis

Qualitative variables were summarized with absolute and relative (percentage) frequencies. Parametric and non-parametric quantitative variables were described with means (standard deviations, SD) and medians (interquartile ranges, IQR), respectively. Chi-squared or Fisher exact test were used to compare qualitative variables, whereas Student t test or Mann-Whitney, ANOVA or Kruskall-Wallis were used to compare quantitative variables with normal or non-normal distribution, respectively. Cox proportional hazard regression analysis was performed to assess the relationship between clinical outcomes and independent variables. A two-tailed p-value less than 0.05 was considered statistically significant. All statistical computations were performed with the statistical software STATA version 16 (StatsCorp, Texas, USA).

RESULTS

Clinical characteristics of the whole sample size

A total of 412 patients were enrolled (280 males, 68%) (Table 1). The median (interquartile range – IQR) age at admission was 66 (55-76) years, and 54.6% of patients were ≥ 65 years old. 61.8% of patients had a PaO2/FiO2 <300 mmHg, with a median (IQR) PaO2/FiO2 of 262 (140-343) mmHg. 24.4% had mild, 21.9% moderate, and 15.5% severe respiratory failure. CPAP was prescribed in the emergency department in 9.7% of cases, whereas only 3 patients were immediately intubated. Median (IQR) white blood cell (WBC) count was 6.7 (5.1-9.4) per 10^9/μL, 10.9% had leukopenia, and 45.9% had lymphocytopenia. Median (IQR) D-dimer values were 890.5 (470-2,157) mg/L FEU, and 34% had a D-dimer >1,000 mg/L FEU (Table 1).

Table 1. Characteristics and outcomes of patients at admission.

	Covid-19 patients

		(n= 412)
Age at admission, years		66 (55-76)
Males, n (%)		280 (68.0)
SARS-COV-2 positive swab, n (%)		412 (100.0)
PaO2/FiO2 at admission, mmHg		262 (140-343)
PaO2/FiO2 severity, n (%)	≤ 100, mmHg	64 (15.5)
	101-200, mmHg	90 (21.9)
	201-300, mmHg	101 (24.4)
	>300, mmHg	157 (38.2)
Respiratory support at admission, n (%)	Room air	125 (30.3)
	Nasal cannulae	93 (22.6)
	Venturi mask	78 (18.9)
	Reservoir mask	68 (16.5)
	CPAP	40 (9.7)
	NIV	5 (1.2)
	IMV	3 (0.7)
BLOOD COUNT and BIOCHEMISTRY		
Haemoglobin, g/l (n= 401)		13.4 (12.4-14.6)
Platelets, per 10^9/uL (n=401)		203 (156-270)
Platelets <100 per 10^9/uL, n (%) (n=401)		17 (4.1)
White blood cells, per 10^9/uL (n=401)		6.7 (5.1-9.4)
White blood cells < 4.0 per 10^9/uL, n (%) (n=401)		45 (10.9)
Neutrophils, per 10^9/uL (n=401)		5.1 (3.3-8.1)
Neutrophils <1.5 per 10^9/uL, n (%) (n=401)		7 (1.7)
Lymphocytes, per 10^9/uL (n=401)		0.98 (0.67-1.33)
Lymphocytes < 1.0 per 10^9/uL, n (%) (n=401)		189 (45.9)
Lymphocytes < 0.5 per 10^9/uL, n (%) (n=401)		44 (10.7)
Blood urea nitrogen, mg/dl (n=372)		37.5 (27-56)
Creatinine, mg/dl (n=401)		0.93 (0.75-1.19)
Creatinine >1.2 mg/dl, n (%) (n=401)		95 (23.1)
D-dimer, mg/L FEU (n=400)		890.5 (470-2,157)
D-dimer ≥ 1,000 mg/L FEU, n (%)		140 (34.0)

(n=195)		
Troponin T, ng/l (n=125)		13 (7.0-22.4)
C-reactive protein, mg/l (n=400)		84.6 (36.2-158.0)
Albumin, g/l (n=151)		28 (23-35)
Interleukin 6 pg/ml (n=83)		86 (31-693)
Ferritin, ug/l (n=145)		1063 (408-2145)
COMORBIDITIES		
Cardiovascular Diseases		
Any cardiovascular disease*, n (%)		207 (50.2)
Hypertension, n (%)		160 (38.8)
Arrhythmia, n (%)		49 (11.9)
Ischaemic heart disease, n (%)		43 (10.4)
Vasculopathy, n (%)		32 (7.8)
Heart failure, n (%)		17 (4.1)
Valvulopathy, n (%)		15 (3.6)
Other		
Diabetes mellitus, n (%)		69 (16.8)
Endocrinology disease, n (%)		57 (13.9)
Neurological disease, n (%)		49 (11.9)
Immune depression, n (%)		39 (9.5)
Hypothyroidism, n (%)		32 (7.8)
Kidney disease, n (%)		31 (7.5)
Orthopaedic disease, n (%)		31 (7.5)
Gastrointestinal disease, n (%)		28 (6.8)
Severe obesity, n (%)		26 (6.3)
COPD, n (%)		25 (6.1)
CKD, n (%)		25 (6.1)
BPH, n (%)		25 (6.1)
Active solid cancer, n (%)		20 (4.9)
Previous cancer, n (%)		18 (4.4)
Stroke, n (%)		17 (4.1)
Other neurological disease, n (%)		14 (3.4)
Asthma, n (%)		13 (3.2)
CHRONIC TREATMENTS		
ACEi at admission, n (%)		59 (14.3)
ACEi name, n (%)	Ramipril	34 (56.7)
	Enalapril	16 (26.7)
	Lisinopril	3 (5.0)
	Perindopril	3 (5.0)
	Zofenpril	2 (3.3)
	Captopril	1 (1.7)
	Zanipril	1 (1.7)

ARBs, n (%)		61 (14.8)
ARB name, n (%)	Olmesartan	25 (39.7)
	Telmisartan	11 (17.5)
	Valsartan	11 (17.5)
	Irbersartan	10 (15.9)
	Losartan	6 (9.5)
ACEi or ARBs, n (%)		119 (28.9)
IN-HOSPITAL TREATMENTS		
Hydroxychloroquine, n (%)		336 (81.6)
Lopinavir/ritonavir, n (%)		242 (58.7)
Corticosteroids, n (%)		105 (25.5)
LMWH, n (%)		249 (60.4)
Tocilizumab, n (%)		88 (21.6)
Experimental drugs, n (%)**		3 (0.7)
OUTCOMES		
CPAP during hospitalization, n (%)		176 (42.7)
CPAP max PEEP		10 (10.0-12.5)
Discharge at home, n (%)		180 (43.7)
Discharge other facility, n (%)		41 (10.0)
Death, n (%)		105 (25.5)
Intubation, n (%)		36 (8.7)
Still hospitalized, n (%)		50 (12.1)

Demographic, clinical characteristics, respiratory failure parameters at admission, and clinical outcomes in 412 patients hospitalized with Covid-19 pneumonia. Data are expressed as frequencies or medians (inter quartile range – IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in Table 1 in *Supplemental material*. Missing values, if presented, are reported next to each variable. ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; NIV: non invasive ventilation; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure; RF: respiratory failure. *at least one of the following 6 categories; **Remdesivir

Half of the patients (50.2%) showed cardiovascular comorbidities, with hypertension being the most prevalent (38.8%). Diabetes and chronic kidney disease were observed in 16.8% and 13.6% of the

cases, respectively. Chronic obstructive pulmonary disease (COPD) and asthma accounted for the 6.1% and 3.2% of the study sample. A complete list of observed comorbidities is reported in Table 1 in Supplemental material.

The most frequently administered therapy was hydroxychloroquine (81.6%), whereas corticosteroids and tocilizumab were prescribed in 25.5% and 21.6% of the patients, respectively.

During the hospital stay, 42.7% were exposed to CPAP, 8.7% underwent mechanical ventilation and were transferred to the ICU.

Characteristics based on severity of respiratory failure

The cohort was divided in four groups based on the severity of respiratory failure (Table 2). Advanced age and male were more prevalent in patients with severe respiratory failure (p-value= 0.0001 and 0.02, respectively). The initiation of CPAP in the emergency department was more frequent in the severe group (22.2%; p-value= 0.0001).

WBC, neutrophils, c-reactive protein, and D-dimer values were higher in severe cases (all p-values= 0.0001). Impaired gas exchange was associated with a decreased lymphocyte counts, ranging from a median (IQR) value of 1.13 (0.84-1.50) per 10^9/μL in patients with PaO2/FiO2 >300 mmHg to 0.74 (0.57-0.99) per 10^9/μL in patients with severe respiratory failure (p-value= 0.0001).

Table 2. Patients' characteristics and outcomes depending on the severity of respiratory failure.

VARIABLES		Severe (P/F ≤100 mmHg) (n= 63)	Moderate (P/F 101-200 mmHg) (n= 89)	Mild (P/F 201-300 mmHg) (n= 99)	Normal (P/F >300 mmHg) (n= 155)	p-value
Age at admission, years		75 (64-81)	72 (63-81)	67 (57-76)	58 (48-70)	0.0001(1)
Males, n (%)		51 (81.0)	67 (75.3)	65 (65.7)	95 (61.3)	0.02(2)
Respiratory support at admission, n	Room air	1 (1.6)	5 (5.6)	23 (23.2)	93 (60.0)	<0.0001(3)
	Nasal cannulae	11 (17.5)	14 (15.7)	32 (32.3)	35 (22.6)	0.03(4)

(%)	Venturi mask	6 (9.5)	27 (30.3)	23 (23.2)	20 (12.9)	0.001[5]
	Reservoir mask	29 (46.0)	31 (34.8)	5 (5.1)	3 (1.9)	<0.0001[6]
	CPAP	14 (22.2)	9 (10.1)	13 (13.1)	4 (2.6)	<0.0001[7]
	NIV	1 (1.6)	2 (2.3)	2 (2.0)	0 (0.0)	0.16
	IMV	1 (1.6)	1 (1.1)	1 (1.0)	0 (0.0)	0.26
BLOOD COUNT						
Haemoglobin, g/l		13.4 (12.5-14.5)	12.9 (11.8-14.6)	13.4 (12.5-14.7)	13.7 (12.7-14.8)	0.05
Platelets, per 10^9/uL		206 (151-286)	225 (160-292)	205.5 (161-264)	192 (152-247)	0.12
White blood cells, per 10^9/uL		8.3 (6.2-12.2)	8.1 (6.0-11.0)	6.5 (5.1-9.0)	5.9 (4.8-7.7)	0.0001[8]
Neutrophils, per 10^9/uL		6.9 (5.0-10.7)	7.0 (4.5-10.0)	4.9 (3.2-7.3)	4.0 (3.0-5.6)	0.0001[9]
Lymphocytes, per 10^9/uL		0.74 (0.57-0.99)	0.84 (0.62-1.14)	1.07 (0.65-1.37)	1.13 (0.84-1.50)	0.0001[10]
Blood urea nitrogen, mg/dl		55 (39-74)	49 (34-78)	37 (29-52)	29 (23-39)	0.0001[11]
Creatinine, mg/dl		0.91 (0.8-1.3)	1.04 (0.76-1.39)	0.92 (0.74-1.15)	0.89 (0.72-1.05)	0.007[12]
D-dimer, mg/L FEU		1990 (701-6210)	1355 (814-4025)	971 (556-1830)	579 (336-953)	0.0001[13]
Troponin T, ng/l		20 (15-44)	15.5 (9.0-31.5)	14 (9-18)	8 (6-12)	0.0001[14]
C-reactive protein, mg/l		153 (86-219)	119 (59-198)	94.2 (40.5-148)	44.2 (20-89.7)	0.0001[15]
Albumin, g/l		24 (20-37)	27 (22-59)	27 (23-34)	31 (27-34)	0.004[16]
Interleukin 6, pg/ml		167 (44-968)	309 (42-1,113)	64 (27-496)	47 (23-183)	0.003[17]
Ferritin, ug/l		1271 (499-2653)	958 (423-2184)	1513.5 (817-2824)	775 (238-1484)	0.06
COMORBIDITIES						
Cardiovascular Diseases						
Cardiovascular disease*, n (%)		38 (60.3)	59 (66.3)	56 (56.6)	51 (32.9)	<0.0001[18]
Hypertension, n (%)		30 (47.6)	42 (47.2)	47 (47.5)	39 (25.2)	<0.0001[19]
Ischaemic heart disease, n (%)		8 (12.7)	14 (15.7)	11 (11.1)	8 (5.2)	0.05
Arrythmia, n (%)		8 (12.7)	16 (18.0)	9 (9.1)	14 (9.0)	0.16
Vasculopathy, n (%)		8 (12.7)	8 (9.0)	9 (9.1)	7 (4.5)	0.19
Valvulopathy, n (%)		2 (3.2)	5 (5.6)	3 (3.0)	4 (2.6)	0.67
Heart failure, n (%)		3 (4.8)	7 (7.9)	4 (4.0)	2 (1.3)	0.07
Other						
Diabetes mellitus, n (%)		9 (14.3)	21 (23.6)	20 (20.0)	18 (11.6)	0.07
Endocrinology disease, n (%)		7 (11.1)	17 (19.1)	13 (13.1)	18 (11.7)	0.37
Neurological disease, n (%)		8 (12.7)	16 (18.0)	13 (13.1)	12 (7.7)	0.12
Immune depression, n (%)		3 (4.8)	12 (13.5)	11 (11.1)	12 (7.7)	0.24
Hypothyroidism, n (%)		2 (3.2)	9 (10.1)	9 (9.1)	10 (6.5)	0.35
Kidney disease, n (%)		5 (7.9)	8 (9.0)	7 (7.1)	8 (5.2)	0.70

Orthopaedic disease, n (%)		3 (4.8)	7 (7.9)	8 (8.1)	13 (8.4)	0.86
Gastrointestinal disease, n (%)		6 (9.5)	8 (9.0)	4 (4.0)	10 (6.5)	0.42
Severe obesity, n (%)		6 (9.5)	12 (13.5)	1 (1.0)	7 (4.5)	0.002[20]
COPD, n (%)		7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04[21]
CKD, n (%)		3 (4.8)	9 (10.1)	5 (5.1)	6 (3.9)	0.26
BPH, n (%)		7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04[22]
Active solid cancer, n (%)		2 (3.2)	7 (7.9)	4 (4.0)	7 (4.5)	0.59
Previous cancer, n (%)		4 (6.4)	4 (4.5)	2 (2.0)	8 (5.2)	0.52
Stroke, n (%)		3 (4.8)	6 (6.7)	4 (4.0)	4 (2.6)	0.44
Other neurological disease, n (%)		4 (6.4)	5 (5.6)	4 (4.0)	1 (0.7)	0.03[23]
Asthma, n (%)		1 (1.6)	3 (3.4)	4 (4.0)	5 (3.2)	0.90
CHRONIC TREATMENTS						
ACEi at admission, n (%)		12 (19.1)	13 (14.6)	24 (24.2)	9 (5.8)	<0.0001[24]
ACEi name, n (%)	Ramipril	6 (50.0)	9 (64.3)	13 (54.2)	5 (55.6)	0.90
	Enalapril	2 (16.7)	3 (21.4)	8 (33.3)	3 (33.3)	0.71
	Lisinopril	1 (8.3)	1 (7.1)	1 (4.2)	0 (0.0)	-
	Perindopril	1 (8.3)	1 (7.1)	0 (0.0)	1 (11.1)	
	Zofenpril	1 (8.3)	0 (0.0)	1 (4.2)	0 (0.0)	
	Captopril	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	Zanipril	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	
ARBs, n (%)		9 (14.3)	16 (18.0)	10 (10.1)	26 (16.8)	0.41
ARB name, n (%)	Olmesartan	6 (66.7)	6 (35.3)	2 (20.0)	11 (40.7)	0.23
	Telmisartan	1 (11.1)	3 (17.7)	3 (30.0)	4 (14.8)	0.71
	Valsartan	1 (11.1)	4 (23.5)	1 (10.0)	5 (18.5)	0.84
	Irbesartan	0 (0.0)	3 (17.7)	3 (30.0)	4 (14.8)	-
	Losartan	1 (1.1)	1 (5.9)	1 (10.0)	3 (11.1)	
ACEi or ARBs, n (%)		21 (33.3)	29 (32.6)	34 (34.3)	34 (21.9)	0.10
IN-HOSPITAL TREATMENTS						
Lopinavir/ritonavir, n (%)		40 (63.5)	50 (56.2)	64 (64.6)	87 (56.1)	0.45
Hydroxychloroquine, n (%)		51 (81.0)	74 (83.2)	89 (89.9)	120 (77.4)	0.09
Corticosteroids, n (%)		26 (41.3)	37 (41.6)	24 (24.2)	18 (11.6)	<0.0001[25]
Tocilizumab, n (%)		17 (27.0)	21 (23.6)	27 (27.3)	22 (14.2)	0.03[26]
LMWH, n (%)		48 (76.2)	66 (74.2)	62 (62.6)	73 (47.1)	<0.0001[27]
Experimental drugs, n (%)		1 (1.6)	0 (0.0)	0 (0.0)	2 (1.3)	0.74
OUTCOMES						
CPAP during hospitalization, n (%)		45 (71.4)	50 (56.2)	49 (49.5)	32 (20.7)	<0.0001[28]
Median (IQR) CPAP max PEEP		12 (10-14)	10 (10.0-12.3)	10 (10.0-12.5)	10 (10.0-12.5)	0.02[29]
Intubation, n (%)		11 (17.5)	5 (5.6)	9 (9.1)	11 (7.1)	0.06
In hospital death, n (%)		35 (55.6)	43 (48.3)	16 (16.2)	10 (6.5)	<0.0001[30]
Days from admission to death		15 (6-37)	25 (7-34)	35 (24-41)	36 (30-41)	0.0001[31]

*at least one of the following 6 categories

1. Severe VS Mild p-value= 0.02; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
2. Severe VS. Mild p-value= 0.04; Severe VS. Normal p-value= 0.005; Moderate VS. Normal p-value= 0.03.
3. Severe VS. Mild p-value= 0.0002; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value= 0.0007; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
4. Severe VS. Mild p-value= 0.04; Moderate VS. Mild p-value= 0.008.
5. Severe VS. Moderate p-value= 0.002; Severe VS. Mild p-value= 0.03; Moderate VS. Normal p-value= 0.0009; Mild VS. Normal p-value= 0.03.
6. Severe VS. Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value <0.0001; Moderate VS. Normal p-value <0.0001.
7. Severe VS. Moderate p-value= 0.04; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value 0.01; Mild VS. Normal p-value 0.001.
8. Severe VS Mild p-value= 0.03; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001.
9. Severe VS Mild p-value= 0.008; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value= 0.01; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.02.
10. Severe VS Mild p-value= 0.01; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value= 0.0006.
11. Severe VS Mild p-value= 0.002; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value= 0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0006.
12. Moderate VS. Normal p-value= 0.004.
13. Severe VS Mild p-value= 0.02; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value=0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.003.
14. Severe VS Normal p-value <0.0001; Moderate VS: Normal p-value=0.001; Mild VS. Normal p-value= 0.01.
15. Severe VS Mild p-value= 0.003; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0002.
16. Severe VS. Normal p-value= 0.002.
17. Severe VS. Normal p-value= 0.02; Moderate VS: Normal p-value=0.004.
18. Severe VS. Normal p-value= 0.0002; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0002.
19. Severe VS. Normal p-value= 0.001; Moderate VS. Normal p-value= 0.0004; Mild VS. Normal p-value= 0.0003.
20. Severe VS. Moderate p-value= 0.009; Moderate VS. Mild p-value= 0.0007; Moderate VS. Normal p-value= 0.01; Mild VS. Normal p-value= 0.01.
21. Severe VS. Normal p-value= 0.02; Moderate VS. Normal p-value= 0.03.
22. Severe VS. Normal p-value= 0.02; Moderate VS. Normal p-value= 0.03.
23. NA
24. Severe VS. Normal p-value= 0.003; Moderate VS. Normal p-value= 0.02; Mild VS. Normal p-value <0.0001.

25. Severe VS Mild p-value= 0.02; Severe VS. Normal p-value <0.0001; Moderate VS Mild p-value= 0.01; Mild VS. Normal p-value= 0.008.
26. Severe VS. Normal p-value= 0.03; Mild VS. Normal p-value= 0.01.
27. Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value= 0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
28. Severe VS. Mild p-value= 0.006; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
29. Severe VS Moderate p-value= 0.005.
30. Severe VS. Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.01.
31. Severe VS Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001.

Data are expressed as frequencies or medians (inter quartile range – IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in Table 1 in *Supplemental material*. ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure.

The proportion of patients with cardiovascular comorbidities and hypertension was significantly higher in patients with a respiratory failure if compared with that of patients with a PaO2/FiO2 >300 mmHg (p-value <0.0001). Obesity was more prevalent in patients with moderate and severe respiratory failure if compared with obesity prevalence in patients with PaO2/FiO2 ≥201 mmHg (23% VS. 5.5%; p-value= 0.002); similar differences were found for COPD (22.2% VS. 7.2%; p-value= 0.04). Chronic use of ACEi was more prevalent in patients with respiratory failure (p-value <0.0001).

Tocilizumab and LMWH were more frequently administered in patients with a PaO2/FiO2 <300 mmHg (p-value=0.03 and <0.0001, respectively). The proportion of patients with moderate and severe respiratory failure exposed to corticosteroids was significantly higher if compared with patients with a mild form (41.6% and 41.3% VS. 24.2%; p-value=0.01 and 0.02, respectively).

The highest proportion of intubated patients was in the severe group (17.5%) (Table 2).

Impact of cardiovascular diseases and RAA system inhibitors

Overall, chronic therapy with ACEi was associated with worse PaO2/FiO2 at admission (median value 223.5 VS. 273.0; p-value= 0.004) (Table 2 in *Supplemental material*) and higher in-hospital mortality (35.6% VS. 23.5%; p-value= 0.048) (Table 2 in *Supplemental material* and Figure 2). Severity of respiratory failure at admission, intubation and mortality rates were not associated with ARBs therapy (Table 3 in *Supplemental material* and Figure 2).

Patients with CVD or hypertension had significantly lower PaO2/FiO2 at admission (both p-values <0.0001), a higher proportion of respiratory failure (both p-values <0.0001), and an increased need for CPAP during the hospital stay (p-value=0.02 and 0.003, respectively) (Table 3 and *Supplemental material* Table 4).

Table 3. Respiratory failure and outcomes in patients with cardiovascular disease, depending on ACEi and ARBs exposure.

	Covid-19 patients (n = 412)								
	CVD No (n= 205)	CVD yes (n= 207)	p-value						
				CVD yes (n= 207)					
				ACEi No (n= 154)	ACEi Yes (n= 53)	p-value	ARBs No (n= 147)	ARBs Yes (n= 60)	p-value
PaO2/FiO2 at admission	307.5 (180-381)	206.5 (123-305)	<0.0001	203 (127-319)	228 (113-290)	0.62	201.5 (118.0-285.5)	285.5 (135-343)	0.01
RF at admission, n (%)	125 (61.0)	174 (84.1)	<0.0001	129 (83.8)	45 (84.9)	0.85	128 (87.1)	46 (76.7)	0.06
CPAP at admission, n (%)	16 (7.8)	24 (11.6)	0.19	20 (13.0)	4 (7.6)	0.29	17 (11.6)	7 (11.7)	0.98
CPAP in-hospital, n (%)	76 (37.1)	100 (48.3)	0.02	75 (48.7)	25 (47.2)	0.85	71 (48.3)	29 (48.3)	1.00
In-hospital mortality, n (%)	32 (15.6)	72 (34.8)	<0.0001	53 (34.4)	19 (35.9)	0.85	58 (39.5)	14 (23.3)	0.03
Intubation, n (%)	23 (11.2)	13 (6.3)	0.08	9 (5.8)	4 (7.6)	0.74	9 (6.1)	4 (6.7)	1.00

Data are reported as frequencies or medians (interquartile range – IQR). CVD: cardiovascular disease; ACEi: angiotensin converting enzyme inhibitor; ARBs: angiotensin receptor blockers. PaO2: arterial partial pressure of oxygen; FiO2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

In hospital mortality and respiratory failure

In-hospital mortality was 25.5%. It proportionally increased with lower PaO2/FiO2 values, being highest in the severe group (55.6%) and lowest in patients with PaO2/FiO2 >300 mmHg (6.5%; p-value <0.0001). The number of days from admission to death was lowest in the severe group and highest in patients with normal PaO2/FiO2 at admission (p-value= 0.0001) (Table 2). Age, male sex, exposure to ACEi, having a CVD, respiratory failure, a lower PaO2/FiO2, and need for CPAP at admission were significantly associated with an increased mortality at the univariate analysis (Table 4); however, the multivariate analysis showed that the only independent risk factors were older age (Hazard rate (HR) 1.1; 95% confidence interval (CI): 1.1-1.1, p-value <0.0001) and the severity of respiratory failure at admission (HR 0.99; 95%CI: 0.99-0.99, p-value <0.0001). Survival rate decreased with increasing respiratory failure severity (p-value <0.0001) (Figure 1). Ten days post admission, patients with moderate and severe respiratory failure had a comparable survival rate (35%), which decreased (50%) at day 18 in the severe group, whereas moderate patients had a survival rate of 42% (Figure 1).

Table 4. Risk factors for in-hospital mortality.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age. years	1.1 (1.1-1.1)	<0.0001	1.1 (1.1-1.1)	<0.0001
Male	1.6 (1.0-2.5)	0.049	1.4 (0.9-2.3)	0.16
Exposure to ACEi	1.7 (1.0-2.7)	0.04	1.1 (0.7-1.69)	0.69
Exposure to ARBs	0.9 (0.5-1.6)	0.76		
Exposure to ACEi or ARBs	1.3 (0.9-2.0)	0.17		
Cardiovascular disease	2.5 (1.6-3.8)	<0.0001	1.2 (0.8-1.9)	0.44
PaO2/FiO2 at admission	0.99 (0.99-0.99)	<0.0001	0.99 (0.99-0.99)	<0.0001
Respiratory failure at admission	15.1 (4.8-47.6)	<0.001	2.2 (0.6-7.9)	0.22
CPAP at admission	2.2 (1.3-3.7)	0.002	1.4 (0.8-2.3)	0.21

Note that for any unit increase of PaO2/FiO2 ratio, patients experience a reduction of 1% in death risk (patients with PaO2/FiO2 ratio of 190 have a 10% increased risk of death compared with patients with a PaO2/FiO2 ratio of 200) HR: hazard ratio.

DISCUSSION

To the best of our knowledge, the results of the present study demonstrated for the first time the independent relationship between impaired gas exchange and clinical outcomes (mortality, intubation, and need for respiratory support).

We showed that younger age and a higher PaO2/FiO2 are independently associated with a higher survival rate. Moreover, patients with a PaO2/FiO2 >300 mmHg had an in-hospital mortality of 6.5%, which was significantly lower if compared with that of patients with mild respiratory failure (16.2%). Mortality increased in patients with moderate hypoxemia (48.3%) and in severe patients exceeded 55%. The overall mortality rate in our cohort is comparable to previous reports.[5,24] However, it is higher if compared with the mortality described in other observational studies.[25,26] Richardson and coworkers reported a prevalence of respiratory failure (SpO2 <90%) of 20.4%,[25] whereas it was 72.6% in our cohort. Cheng et al. reported an in-hospital mortality as low as 11% in Wuhan, China. However, 58% of enrolled patients were not discharged from hospital at the time of the report,[26] whereas only 12% of our cohort was hospitalized at the time of writing.

Hypoxemia has been rarely considered as a risk factor for COVID-19 patients' outcome. Xie and colleagues showed that patients with SpO2 <90% had 47 times more the probability to die when compared with patients with SpO2 >90%.[27] However, in patients with COVID-19 associated pneumonia, low PaO2 values can be associated with satisfactory SpO2, hiding hypoxia, which might lead to an underestimation of the severity of the disease and in a treatment delay.[28] On this basis, clinicians should not rely solely on SpO2 values, especially when evaluating patients in which symptoms had lasted for 10-12 days before their presentation to the emergency department.[29] The ratio between PaO2 and FiO2 has been demonstrated to be a reliable tool to assess severity and stratify mortality risk.[17] When compared with the ARDS Berlin's definition, our respiratory failure classes had a slightly higher mortality with PaO2/FiO2 <200 mmHg (severe 55% VS. 45% and moderate 48% VS. 35%). This should probably depend on the cohort heterogeneity and in, in our case, the absence of 5 cmH2O of PEEP used in the Berlin definition to grade severity of ARDS. Another issue is the low number of patients with severe respiratory failure at admission who

underwent intubation (n= 11). This finding can be justified by the higher chance of DNI orders in patients with severe respiratory failure, secondary to the median age and to the higher prevalence of CVD.[5] However, the absence of respiratory failure at admission or a mild hypoxia did not preclude the chance of in-hospital death or intubation. Sign of respiratory distress and worsening gas exchange should be closely monitored, as a sudden and rapidly evolving disease can involve patients in stable conditions.[29, 30]

CVD and hypertension are the most frequently observed comorbidities in patients with COVID-19 and are associated with severe disease.[31, 32] A debate was focused on the negative effects of ACEi and ARBs due to the role of the ACE2 receptor in viral-host dynamics.[32] However, several studies ruled out the increased risk of COVID-19 infection and the link between disease severity and antihypertensive treatment.[28,31,33] Our cohort was characterized by a high prevalence of CVD (50.2%), which was associated with a significantly higher mortality compared with patients without CVD. However, mortality did not change in patients chronically exposed to ACEi and ARBs. ACEi was associated with a significantly higher mortality, potentially explained by the higher disease severity of at admission of patients taking ACEi. Indeed, neither CVD, nor hypertension, nor the exposure to antihypertensive medications were independently associated with decreased survival.

Study limitations

The initial gas exchange assessment was not homogeneously conducted in all patients at admission (only 30.3% of patients were in room air conditions). This might have underestimated the severity of respiratory failure, especially in patients treated with CPAP at admission. At the time of writing, 12% of patients were still hospitalized, biasing mortality and length of stay estimates. Furthermore, a selection bias could be hypothesized, being the participating centres hub for severe patients transferred from peripheral hospitals. The local standard operating procedures, criteria for ICU admittance or management with CPAP/NIV implemented in Italy could differ in other settings, limiting the inference of our findings.

CONCLUSIONS

The severity of respiratory failure assessed with the PaO2/FiO2 ratio is significantly associated with intubation rate, need for respiratory support, and in-hospital mortality. The PaO2/FiO2 value at admission is independently associated with in-hospital mortality, and should be always assessed and monitored throughout the hospital stay, even in clinical stability. Clinical severity criteria of patients with COVID-19 pneumonia should be re-considered based on severity of hypoxemia.

DATA AVAILABILITY

P.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the decision to submit for publication. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHORS' CONTRIBUTIONS

P.S. and D.R. conceived the study and contributed to data collection, analysis and interpretation. G.S. performed the data analysis and contributed to study design and interpretation. L.S. performed the analysis and contributed to data interpretation. P.M., C.C., G.D.F., M.R., E.F., S.P., F.G., M.D.M., G.N., V.V. AND F.T. contributed to data collection and interpretation. P.S., D. R., G.S. and L.S. drafted and revised the manuscript. All authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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The corresponding author here confirms that he has listed everyone who contributed significantly to the work.

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FIGURES' LEGENDS

Figure 1. Survival in patients hospitalized for COVID-19 based on respiratory failure severity

Hazard ratio for survival in patients hospitalized with COVID-19 pneumonia grouped by severity of respiratory failure at admission. Note that after 18 days from admission, patients with severe respiratory failure had a survival rate of 50%. PaO2/FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio.

Figure 2. Survival curves based on ACEi or ARBs exposure

Survival in patients hospitalized with COVID-19 pneumonia (n = 412) based on the chronic exposure to ACEi (angiotensin converting enzyme inhibitors, upper panel) or angiotensin receptor blockers (ARBs, lower panel).

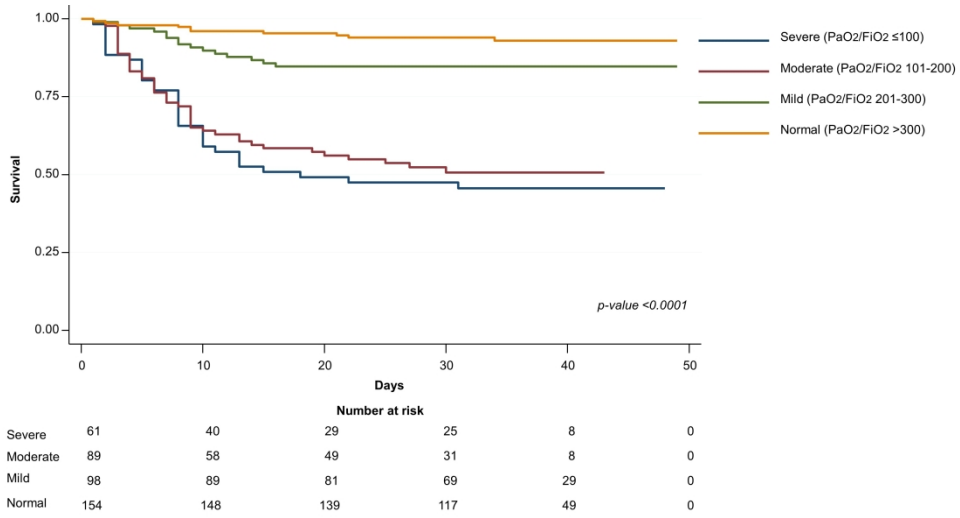

Figure 1. Survival in patients hospitalized for COVID-19 based on respiratory failure severity
Hazard ratio for survival in patients hospitalized with COVID-19 pneumonia grouped by severity of respiratory failure at admission. Note that after 18 days from admission, patients with severe respiratory failure had a survival rate of 50%. PaO2/FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio.

338x190mm (300 x 300 DPI)

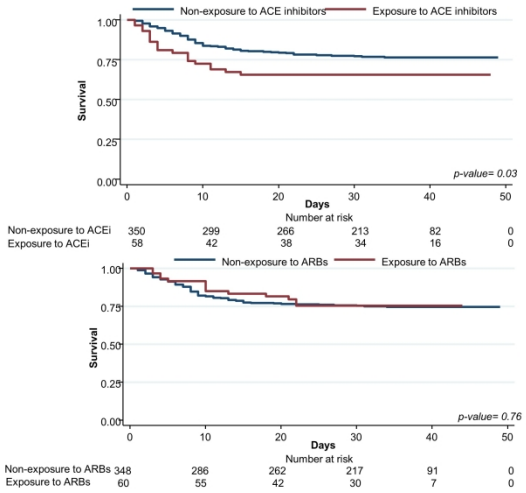

Figure 2. Survival curves based on ACEi or ARBs exposure
Survival in patients hospitalized with COVID-19 pneumonia (n = 412) based on the chronic exposure to ACEi (angiotensin converting enzyme inhibitors, upper panel) or angiotensin receptor blockers (ARBs, lower panel).

338x190mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

TITLE: HOW SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AFFECTS IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY

Participating centers

1. Division of Respiratory Diseases, Ospedale L. Sacco, ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy.
2. Department of Medicine and Rehabilitation, Division of Emergency Medicine, Ospedale Fatebenefratelli - ASST Fatebenefratelli-Sacco, Piazzale Principessa Clotilde, 3 - 20121 Milano, Italy.
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4. Department of Health Bioscience, Università degli Studi di Milano—Respiratory Unit, Policlinico di San Donato, IRCCS— Via Rodolfo Morandi, 30 - 20097, San Donato Milanese, Milano, Italy.

The study protocol is available at: ClinicalTrials.gov: NCT04307459

Definition of immunocompromission

Immunocompromission was defined as the presence of ≥1 of the following risk factors:[1]

1. Acquired Immuno-Deficiency Syndrome (AIDS), defined either as human immunodeficiency virus infection with CD4+ lymphocyte count <200/μL or by the occurrence of AIDS-defining conditions;
2. aplastic anemia;
3. asplenia;
4. hematological cancer, defined as lymphoma, acute or chronic leukemia, or multiple myeloma;
5. chemotherapy during the last 3 months;

6. neutropenia, defined as a neutrophil count <500/dL at complete blood cell count;
7. biological drug use (including trastuzumab and therapies for autoimmune diseases, e.g., anti–tumor necrosis factor α, prescribed during ≥6 months before hospital admission);
8. lung transplantation;
9. chronic steroid use (>10 mg/d of prednisone or equivalent ≥3 months before hospital admission);
10. lung cancer with either neutropenia or chemotherapy;
11. other solid tumor with either neutropenia or chemotherapy;
12. other immunocompromise (any immunocompromised state, including congenital/genetic immunocompromised and immunosuppressive therapy due to hematological cancer/solid organ transplantation other than lung).

Criteria for hospitalization

Hospitalization criteria were based on the standard operating procedures created for the management of patients with suspected Covid-19,[2, 3] and on the latest international recommendations.[4, 5] Criteria included any of the following: 1) the presence of respiratory failure at admission (a PaO2 <60 mmHg while breathing room air or a PaO2/FiO2 ratio <300 mmHg); 2) age >65 years old with one or more comorbidities, pulmonary infiltrates at the chest X-ray or Ct scan and respiratory distress (a respiratory rate ≥ 30 breaths/minute and dyspnea); 3) pulmonary infiltrates and persistence of respiratory symptoms (cough, chest tightness, dyspnea at rest or during effort, fever) for more than 10 days; 4) pulmonary infiltrates with evidence of oxygen desaturation (drop in SpO2 of more than 4 units from resting value) while walking for 3 minutes; 5) hemodynamic instability, sepsis or shock; 6) sepsis and septic shock; 7) pulmonary infiltrates associated with confusion or a Glasgow Coma Scale <15; 8) inability to cope with outpatient therapy due to psychosocial or such as inability to maintain oral intake, history of substance abuse, cognitive impairment, severe comorbid illnesses, and impaired functional status.[5]

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Supplemental Table 1. Complete list of comorbidities observed in the study sample.

COMORBIDITIES	
Hypertension, n (%)	160 (38.8)
Ischaemic heart disease, n (%)	43 (10.4)
Arrythmia, n (%)	49 (11.9)
Vasculopathy, n (%)	32 (7.8)
Valvulopathy, n (%)	15 (3.6)
Heart failure, n (%)	17 (4.1)
Cardiovascular disease*, n (%)	207 (50.2)
Diabetes mellitus, n (%)	69 (16.8)
Severe obesity, n (%)	26 (6.3)
COPD, n (%)	25 (6.1)
Obstructive sleep apnoea syndrome, n (%)	5 (1.2)
Asthma, n (%)	13 (3.2)
Interstitial lung disease, n (%)	1 (0.2)
Active solid cancer, n (%)	20 (4.9)
Active haematological tumour, n (%)	7 (1.7)
Previous cancer, n (%)	18 (4.4)
Anaemia, n (%)	8 (1.9)
Immune depression, n (%)	39 (9.5)
Psychiatric disease, n (%)	12 (2.9)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Kidney disease, n (%)	31 (7.5)
Gastrointestinal disease, n (%)	28 (6.8)
MRGE, n (%)	12 (2.9)
Rheumatology, n (%)	4 (1.0)
Orthopaedic disease, n (%)	31 (7.5)
BPH, n (%)	25 (6.1)
Infectious, n (%)	7 (1.7)
Eye disease, n (%)	9 (2.2)
ORL, n (%)	4 (1.0)
Haematological disease, n (%)	8 (1.9)
Gynaecological disease, n (%)	9 (2.2)
Depression, n (%)	9 (2.2)
Others psychiatric disease, n (%)	5 (1.2)
Hypothyroidism, n (%)	32 (7.8)
Hyperuricemia, n (%)	4 (1.0)
Osteoporosis, n (%)	7 (1.7)
Others endocrinological disease, n (%)	8 (1.9)
Stroke, n (%)	17 (4.1)
Mental disability, n (%)	5 (1.2)
Alzheimer, n (%)	5 (1.2)
Dementia, n (%)	7 (1.7)

Epilepsy, n (%)	8 (1.9)
Others neurological disease, n (%)	14 (3.4)
CKD, n (%)	25 (6.1)
Kidney stones, n (%)	7 (1.7)
Others renal disease, n (%)	7 (1.7)
Cholecystectomy, n (%)	9 (2.2)
Appendectomy, n (%)	9 (2.2)
Gastric/Duodenal ulcer, n (%)	6 (1.5)
Chronic Hepatitis-C, n (%)	6 (1.5)
Others gastro, n (%)	18 (4.4)
Prosthetics, n (%)	12 (2.9)
Hernia, n (%)	14 (3.4)
Others surgery, n (%)	8 (1.9)
Hysterectomy, n (%)	7 (1.7)
Others gynaecology, n (%)	0 (0.0)

BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; ORL: otolaryngology.

Supplemental Table 2. Respiratory failure and outcomes in patients exposed and not exposed to angiotensin converting enzyme inhibitors

	Not-exposure to ACE inhibitors (n= 353)	Exposure to ACE inhibitors (n= 59)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	273 (148.0-346.5)	223.5 (113-290)	0.004
Presence of respiratory failure at admission, n (%)	250 (70.8)	49 (83.1)	0.05
Need for CPAP at admission, n (%)	34 (9.6)	6 (10.2)	0.90
Need for CPAP during the hospital stay, n (%)	148 (41.9)	28 (47.5)	0.43
In-hospital mortality, n (%)	83 (23.5)	21 (35.6)	0.048
Need for intubation, n (%)	31 (8.8)	5 (8.5)	0.94

ACEi: angiotensin converting enzyme inhibitors; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 3. Respiratory failure severity and outcomes in patients exposed and not exposed to angiotensin receptor blockers

	Non-exposure to ARBs (n = 351)	Exposure to ARBs (n= 61)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	262 (140-341)	289 (140-343)	0.98
Presence of respiratory failure at admission, n (%)	252 (71.8)	47 (77.1)	0.40
Need for CPAP at admission, n (%)	32 (9.1)	8 (13.1)	0.33
Need for CPAP during the hospital stay, n (%)	146 (41.6)	30 (49.2)	0.27
In-hospital mortality, n (%)	90 (25.6)	14 (23.0)	0.66
Need for intubation, n (%)	32 (9.1)	4 (6.6)	0.63

ARBs: angiotensin receptor blockers; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 4. Severity of respiratory failure and outcomes in patients with hypertension compared with patients without hypertension.

	Hypertension (n = 160)	No-hypertension (n= 252)	p-value	No-hypertension (n= 252)			
				Without CVD (n=205)	p-value*	With CVD (n= 47)	p-value*
PaO_2/FiO_2 at admission, mmHg	214.5 (120.0-300.0)	291.5 (153.5-362.0)	<0.0001	307.5 (180-381)	<0.0001	184 (126-310)	0.65
Respiratory failure at admission, n (%)	135 (84.4)	164 (65.1)	<0.0001	125 (61.0)	<0.0001	39 (83.0)	0.82
CPAP at admission, n (%)	18 (11.3)	22 (8.7)	0.40	16 (7.8)	0.26	6 (18.8)	0.78
CPAP in-hospital, n (%)	76 (47.5)	100 (39.7)	0.12	76 (37.1)	0.045	24 (51.2)	0.67
In-hospital mortality, n (%)	53 (33.1)	51 (20.2)	0.003	32 (15.6)	<0.0001	19 (40.4)	0.36
Intubation, n (%)	10 (6.3)	26 (10.3)	0.15	23 (11.2)	0.10	3 (6.4)	0.97

A sensitivity analysis has been performed excluding patients with cardiovascular diseases from patients without hypertension**.** PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

* VS. patients with hypertension

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract DONE – page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. DONE – page 3 and 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. DONE – page 6
Objectives	3	State specific objectives, including any prespecified hypotheses. DONE – page 6
Methods		
Study design	4	Present key elements of study design early in the paper. DONE – page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. DONE- page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. DONE- page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed. N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. DONE - page 7 and 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. DONE – page 7 and 8
Bias	9	Describe any efforts to address potential sources of bias. DONE – page 7 and 8
Study size	10	Explain how the study size was arrived at DONE - page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. DONE page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. DONE – page 9
		(*b*) Describe any methods used to examine subgroups and interactions. DONE – page 9
		(*c*) Explain how missing data were addressed. DONE, table 1 (pages 10-12)
		(*d*) If applicable, explain how loss to follow-up was addressed. N/A
		(*e*) Describe any sensitivity analyses. N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. DONE – Page 9
		(b) Give reasons for non-participation at each stage. N/A
		(c) Consider use of a flow diagram. N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. DONE - page 10-12
		(b) Indicate number of participants with missing data for each variable of interest - DONE - page 10-12
		(c) Summarise follow-up time (eg, average and total amount). DONE – page 16-16
Outcome data	15*	Report numbers of outcome events or summary measures over time. DONE – page 15-16 and Figure 1

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. DONE – page 20
		(*b*) Report category boundaries when continuous variables were categorized. DONE – page 20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. DONE – Page 18 and Supplementary material Tables 2 to 4
Discussion		
Key results	18	Summarise key results with reference to study objectives. DONE – Page 21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. DONE – Page 22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. DONE – Page 21-22
Generalisability	21	Discuss the generalisability (external validity) of the study results. DONE – Page 22
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. DONE – Page 23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	COVID-19, Respiratory physiology < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), VIROLOGY, Respiratory infections < THORACIC MEDICINE

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TITLE: SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY.

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ABSTRACT

Objectives: Coronavirus Disease 2019 (COVID-19) causes lung parenchymal and endothelial damage that lead to hypoxic acute respiratory failure (hARF). The influence of hARF severity on patients' outcomes is still poorly understood.

Design: observational, prospective, multicenter study.

Setting: three academic hospitals in Milan (Italy) involving three respiratory high dependency units and three general wards.

Participants: consecutive adult hospitalized patients with a virologically-confirmed diagnosis of COVID-19. Patients with <18 years old or unable to provide informed consent were excluded.

Interventions: anthropometrical, clinical characteristics and blood biomarkers were assessed within the first 24 hours from admission. hARF was graded as follows: severe (partial pressure of oxygen to fraction of inspired oxygen ratio [PaO2/FiO2] <100 mmHg); moderate (PaO2/FiO2 101-200 mmHg); mild (PaO2/FiO2 201-300 mmHg) and normal (PaO2/FiO2 >300 mmHg).

Primary and secondary outcome measures: the primary outcome was the assessment of clinical characteristics and in-hospital mortality based on the severity of respiratory failure. Secondary outcomes were intubation rate and application of continuous positive airway pressure (helmet CPAP) during hospital stay.

Results: 412 patients were enrolled (280 males, 68%). Median (interquartile range – IQR) age was 66 (55-76) years with a PaO2/FiO2 at admission of 262 (140-343) mmHg. 50.2% had a cardiovascular disease (CVD). Prevalence of mild, moderate and severe hRF was 24.4%, 21.9% and 15.5%, respectively. In-hospital mortality proportionally increased with increasing impairment of gas exchange (p-value<0.001). The only independent risk factors for mortality were age ≥65 years (Hazard rate (HR) 3.41; 95% confidence interval (CI): 2.00-5.78, p-value<0.0001), PaO2/FiO2 ratio≤200 mmHg (HR 3.57; 95%CI: 2.20-5.77, p-value<0.0001) and respiratory failure at admission (HR 3.58; 95%CI: 1.05-12.18, p-value=0.04).

Conclusions: A moderate--severe impairment in PaO2/FiO2 was independently associated with a threefold increase in risk of in-hospital mortality. Severity of respiratory failure is useful to identify patients at higher risk of mortality.

Trial registration: NCT04307459

STRENGTHS AND LIMITATIONS (LIMITED TO METHODS)

- This was a multicentre, prospective study
- The study has enrolled a conspicuous of well characterized patients hospitalized with COVID-19 pneumonia
- A selection bias may be due to the high number of severe patients due to the Hub characteristics of the participating centres
- Not all patients were evaluated in room air conditions at admittance, thus potentially underestimating the severity of the study sample

INTRODUCTION

The severe acute respiratory syndrome Coronavirus type 2 (SARS-CoV-2) and the related Coronavirus Disease 2019 (COVID-19) has caused a pandemic and ~860,000 deaths worldwide.[1] The clinical spectrum can range from mild symptoms (e.g., fever and malaise) to severe hypoxic respiratory failure, sepsis, multi-organ involvement, and death. The infection appears to induce an inflammatory reaction with pulmonary infiltrates generating hypoxemia secondary to intra-parenchymal shunt and ventilation/perfusion mismatch, favored by endothelial damage and dysfunction, and altered regulation of perfusion and associated with macro and/or micoembolism.[2,3] So far, risk factors such as older age,[4-6] severity of clinical presentation [4-7], increased D-dimer values,[4] cardiovascular disease (CVD),[4,5] and hypertension [5-8] have been associated with unfavorable outcomes.

It has been proposed that clinical severity of COVID-19 should depend on the presence of any of the following criteria: a partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio <300 mmHg, a respiratory rate >30 per minute, and a peripheral oxygen saturation (SpO2) <93%.[4, 9-12] Several consensus statements recommend different PaO2 and SpO2 thresholds to prescribe continuous positive airway pressure (CPAP),[13-15] non-invasive ventilation, or intubation.[16] Data on the association between severity of respiratory failure at admission and patients' outcomes are still limited.

The aim of the present study was to assess the clinical characteristics of COVID-19 patients based on the severity of respiratory failure, and to explore the relationship between the degree of gas exchange impairment and clinical outcomes (CPAP initiation and mortality).

METHODS

An observational, prospective, multicenter study was conducted in three academic hospitals in Milan (Italy) from March 7 to May 7, 2020, involving three respiratory high dependency units and three general wards. A detailed list of participating centers is reported in the *Supplementary file*. The study protocol (ClinicalTrials.gov: NCT04307459), designed following the amended Declaration of Helsinki (2013), was approved by the local ethical committee (Comitato Etico Milano Area I; 17263/2020) and

all recruited patients gave written informed consent. The authors received no specific funding for this work.

Patient and Public Involvement

Participants were not involved in the design and conduct of the research, interpretation of results and writing of the manuscript. The results of the study will be shared with local patients' organizations by social media and summary reports on organizations' websites.

Patients

Adult hospitalized patients with a virologically-confirmed diagnosis of SARS-CoV-2 infection were considered eligible for study enrolment. Patients with <18 years old or unable to provide informed consent were excluded from the study. Hospitalization criteria are reported in the *Supplementary file.*

Procedures

Anthropometrical and clinical characteristics were collected at admission. The PaO2/FiO2 ratio was calculated from the first available arterial blood gas analysis performed in the emergency department. PaO2/FiO2 thresholds to grade severity of respiratory failure were taken from the Acute Respiratory Distress Syndrome (ARDS) Berlin definition, and were:[17] normal (PaO2/FiO2 >300 mmHg); mild (PaO2/FiO2 201-300 mmHg); moderate (PaO2/FiO2 101-200 mmHg); severe (PaO2/FiO2 ≤100 mmHg). Blood count and biochemistry parameters were assessed during the first 24 hours after hospital admission.

Outcomes

The primary outcome was the description of patients' clinical characteristics at admission and the assessment of in-hospital mortality based on the severity of respiratory failure.

Secondary outcomes were the assessment of intubation rate and application of CPAP during the hospital stay.

Study definitions

SARS-CoV-2 infection and co-infections

The COVID-19 diagnosis was based on a positive nasopharyngeal swab collected in the emergency department. *SARS-CoV-2* infection was proved by means of reverse transcriptase polymerase chain reaction (RT-PCR). In case a first swab was negative, and the clinical picture was highly suggestive for COVID-19, the swab was repeated. Co-infection with *Influenza virus* A and B, A*denovirus*, *human Rhinovirus, Respiratory Syncytial virus*, *human Metapneumovirus* were also investigated and analyzed by means of RT-PCR or rapid influenza diagnostic tests (RIDTs).[18] Microbiological testing for bacteria and fungi in blood, upper and lower airway tract, sputum and urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed according to standard operating protocols.

Management of respiratory failure

Helmet CPAP was the only non invasive respiratory support used in patients with confirmed or suspected COVID-19 pneumonia not responsive to oxygen masks in order to reduce the viral exposure of the healthcare workers in rooms without negative pressure.[19] Patients with a PaO2/FiO2 ratio <300 mmHg in room air were administered oxygen with nasal cannulae to reach a SpO2 of 94% or PaO2 >60 mmHg; in case of unsuccessful intervention within 30 minutes, patients were put on reservoir masks with 90-100% FiO2 or helmet CPAP was initiated with PEEP up to 12 cmH2O based on the respiratory distress and comorbidities following standard operating procedures as previously described.[14] CPAP failure after two hours with the maximal tolerable PEEP and a FiO2 of 100% was considered in case of: a) persistence of PaO2/FiO2<300 mmHg; b) hemodynamic instability (systolic blood pressure <90 mmHg despite adequate fluid support) or altered consciousness; d) respiratory distress, fatigue and/or a respiratory rate >30 bpm.[20] Patients that fulfilled CPAP failure criteria were evaluated by an ICU physician for potential intubation. A do not intubate (DNI) order was established by the treating attending physician following a multidisciplinary discussion with the unit staff and the ICU and based on patient's age, comorbidities and clinical status.

In hospital treatment

Unless contraindicated, patients received hydroxychloroquine and lopinavir/ritonavir following local standard and Italian guidelines.[21,22] In patients with severe pneumonia, methylprednisolone was given at a maximal dose of 1 mg/Kg according to the ATS/IDSA guidelines [23] and local standard operating procedures. Criteria for methylprednisolone initiation included age <80 years, PaO2/FiO2 <250 mmHg, bilateral infiltrates at the chest x-ray or CT scan, a C-reactive protein>100 mg/l, and/or a diagnosis of ARDS according to the Berlin definition [17]. Immunomodulation with off-label tocilizumab at a dosage of 8 mg/Kg body weight was administered in patients with signs of hyper-inflammatory syndrome and elevated IL-6.[21] Unless contraindicated, patients received prophylactic low molecular weight heparin (LMWH) or were switched to therapeutic LMWH dosage if already on chronic anticoagulant therapy. Patients with signs of deep vein thrombosis, pulmonary embolism or D-dimer values >5,000 received a therapeutic dose of LMWH.

Statistical Analysis

Qualitative variables were summarized with absolute and relative (percentage) frequencies. Parametric and non-parametric quantitative variables were described with means (standard deviations, SD) and medians (interquartile ranges, IQR), respectively. Chi-squared or Fisher exact test were used to compare qualitative variables, whereas Student t test or Mann-Whitney, ANOVA or Kruskall-Wallis, corrected with Sidak adjustment, were used to compare quantitative variables with normal or non-normal distribution, respectively. Cox proportional hazard regression analysis was performed to assess the relationship between clinical outcomes and independent variables. A two-tailed p-value less than 0.05 was considered statistically significant. All statistical computations were performed with the statistical software STATA version 16 (StatsCorp, Texas, USA).

RESULTS

Clinical characteristics of the whole sample size

A total of 412 patients were enrolled (280 males, 68%) (Table 1). The median (interquartile range – IQR) age at admission was 66 (55-76) years, and 54.6% of patients were ≥ 65 years old. 61.8% of

patients had a PaO2/FiO2 <300 mmHg, with a median (IQR) PaO2/FiO2 of 262 (140-343) mmHg. 24.4% had mild, 21.9% moderate, and 15.5% severe respiratory failure. CPAP was prescribed in the emergency department in 9.7% of cases, whereas only 3 patients were immediately intubated. Median (IQR) white blood cell (WBC) count was 6.7 (5.1-9.4) per 10^9/µL, 10.9% had leukopenia, and 45.9% had lymphocytopenia. Median (IQR) D-dimer values were 890.5 (470-2,157) mg/L FEU, and 34% had a D-dimer >1,000 mg/L FEU (Table 1).

Table 1. Characteristics and outcomes of patients at admission.

		Covid-19 patients (n= 412)
Age at admission, years		66 (55-76)
Males, n (%)		280 (68.0)
SARS-COV-2 positive swab, n (%)		412 (100.0)
PaO2/FiO2 at admission, mmHg		262 (140-343)
PaO2/FiO2 severity, n (%)	≤ 100, mmHg	64 (15.5)
	101-200, mmHg	90 (21.9)
	201-300, mmHg	101 (24.4)
	>300, mmHg	157 (38.2)
Respiratory support at admission, n (%)	Room air	125 (30.3)
	Nasal cannulae	93 (22.6)
	Venturi mask	78 (18.9)
	Reservoir mask	68 (16.5)
	CPAP	40 (9.7)
	NIV	5 (1.2)
	IMV	3 (0.7)
BLOOD COUNT and BIOCHEMISTRY		
Haemoglobin, g/l (n= 401)		13.4 (12.4-14.6)
Platelets, per 10^9/uL (n=401)		203 (156-270)
Platelets <100 per 10^9/uL, n (%) (n=401)		17 (4.1)
White blood cells, per 10^9/uL (n=401)		6.7 (5.1-9.4)
White blood cells < 4.0 per 10^9/uL, n (%) (n=401)		45 (10.9)
Neutrophils, per 10^9/uL (n=401)		5.1 (3.3-8.1)
Neutrophils <1.5 per 10^9/uL, n (%) (n=401)		7 (1.7)

Lymphocytes, per 10^9/uL (n=401)	0.98 (0.67-1.33)
Lymphocytes < 1.0 per 10^9/uL, n (%) (n=401)	189 (45.9)
Lymphocytes < 0.5 per 10^9/uL, n (%) (n=401)	44 (10.7)
Blood urea nitrogen, mg/dl (n=372)	37.5 (27-56)
Creatinine, mg/dl (n=401)	0.93 (0.75-1.19)
Creatinine >1.2 mg/dl, n (%) (n=401)	95 (23.1)
D-dimer, mg/L FEU (n=400)	890.5 (470-2,157)
D-dimer ≥ 1,000 mg/L FEU, n (%) (n=195)	140 (34.0)
Troponin T, ng/l (n=125)	13 (7.0-22.4)
C-reactive protein, mg/l (n=400)	84.6 (36.2-158.0)
Albumin, g/l (n=151)	28 (23-35)
Interleukin 6 pg/ml (n=83)	86 (31-693)
Ferritin, ug/l (n=145)	1063 (408-2145)
COMORBIDITIES	
Cardiovascular Diseases	
Any cardiovascular disease*, n (%)	207 (50.2)
Hypertension, n (%)	160 (38.8)
Arrhythmia, n (%)	49 (11.9)
Ischaemic heart disease, n (%)	43 (10.4)
Vasculopathy, n (%)	32 (7.8)
Heart failure, n (%)	17 (4.1)
Valvulopathy, n (%)	15 (3.6)
Other	
Diabetes mellitus, n (%)	69 (16.8)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Immune depression, n (%)	39 (9.5)
Hypothyroidism, n (%)	32 (7.8)
Kidney disease, n (%)	31 (7.5)
Orthopaedic disease, n (%)	31 (7.5)
Gastrointestinal disease, n (%)	28 (6.8)
Severe obesity, n (%)	26 (6.3)
COPD, n (%)	25 (6.1)

CKD, n (%)		25 (6.1)
BPH, n (%)		25 (6.1)
Active solid cancer, n (%)		20 (4.9)
Previous cancer, n (%)		18 (4.4)
Stroke, n (%)		17 (4.1)
Other neurological disease, n (%)		14 (3.4)
Asthma, n (%)		13 (3.2)
CHRONIC TREATMENTS		
ACEi at admission, n (%)		59 (14.3)
ACEi name, n (%)	Ramipril	34 (56.7)
	Enalapril	16 (26.7)
	Lisinopril	3 (5.0)
	Perindopril	3 (5.0)
	Zofenpril	2 (3.3)
	Captopril	1 (1.7)
	Zanipril	1 (1.7)
ARBs, n (%)		61 (14.8)
ARB name, n (%)	Olmesartan	25 (39.7)
	Telmisartan	11 (17.5)
	Valsartan	11 (17.5)
	Irbersartan	10 (15.9)
	Losartan	6 (9.5)
ACEi or ARBs, n (%)		119 (28.9)
IN-HOSPITAL TREATMENTS		
Hydroxychloroquine, n (%)		336 (81.6)
Lopinavir/ritonavir, n (%)		242 (58.7)
Corticosteroids, n (%)		105 (25.5)
LMWH, n (%)		249 (60.4)
Tocilizumab, n (%)		88 (21.6)
Experimental drugs, n (%)**		3 (0.7)
OUTCOMES		
CPAP during hospitalization, n (%)		176 (42.7)
CPAP max PEEP		10 (10.0-12.5)
Discharge at home, n (%)		180 (43.7)
Discharge to other facility, n (%)		41 (10.0)
In-hospital mortality, n (%)		105 (25.5)
Intubation, n (%)		36 (8.7)
Still hospitalized, n (%)		50 (12.1)

Demographic, clinical characteristics, respiratory failure parameters at admission, and clinical outcomes in 412 patients hospitalized with Covid-19 pneumonia. Data are expressed as frequencies or medians (inter quartile range – IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in Table 1 of the *Supplementary file.* Missing values, if

present, are reported next to each variable. ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; NIV: non invasive ventilation; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure; RF: respiratory failure. *at least one of the following 6 categories; **Remdesivir

Half of the patients (50.2%) showed cardiovascular comorbidities, with hypertension being the most prevalent (38.8%). Diabetes and chronic kidney disease were observed in 16.8% and 13.6% of the cases, respectively. Chronic obstructive pulmonary disease (COPD) and asthma accounted for the 6.1% and 3.2% of the study sample. A complete list of observed comorbidities is reported in Table 1 of the Supplementary file.

The most frequently administered therapy was hydroxychloroquine (81.6%), whereas corticosteroids and tocilizumab were prescribed in 25.5% and 21.6% of the patients, respectively.

During the hospital stay, 42.7% were exposed to CPAP, 8.7% underwent mechanical ventilation and were transferred to the ICU.

Characteristics based on severity of respiratory failure

The cohort was divided in four groups based on the severity of respiratory failure (Table 2). Advanced age and male were more prevalent in patients with severe respiratory failure (p-value= 0.0001 and 0.02, respectively).

WBC, neutrophils, c-reactive protein, and D-dimer values were higher in severe cases (all p-values = 0.0001). Impaired gas exchange was associated with a decreased lymphocyte counts, ranging from a median (IQR) value of 1.13 (0.84-1.50) per 10^9/μL in patients with PaO2/FiO2 >300 mmHg to 0.74 (0.57-0.99) per 10^9/μL in patients with severe respiratory failure (p-value= 0.0001).

Table 2. Patients' characteristics and outcomes depending on the severity of respiratory failure.

VARIABLES		Severe (P/F ≤100 mmHg) (n= 63)	Moderate (P/F 101-200 mmHg) (n= 89)	Mild (P/F 201-300 mmHg) (n= 99)	Normal (P/F >300 mmHg) (n= 155)	p-value
Age at admission, years		75 (64-81)	72 (63-81)	67 (57-76)	58 (48-70)	0.0001(1)
Males, n (%)		51 (81.0)	67 (75.3)	65 (65.7)	95 (61.3)	0.02(2)
Respiratory support at admission, n (%)	Room air	1 (1.6)	5 (5.6)	23 (23.2)	93 (60.0)	<0.0001(3)
	Nasal cannulae	11 (17.5)	14 (15.7)	32 (32.3)	35 (22.6)	0.03(4)
	Venturi mask	6 (9.5)	27 (30.3)	23 (23.2)	20 (12.9)	0.001(5)
	Reservoir mask	29 (46.0)	31 (34.8)	5 (5.1)	3 (1.9)	<0.0001(6)
	CPAP	14 (22.2)	9 (10.1)	13 (13.1)	4 (2.6)	<0.0001(7)
	NIV	1 (1.6)	2 (2.3)	2 (2.0)	0 (0.0)	0.16
	IMV	1 (1.6)	1 (1.1)	1 (1.0)	0 (0.0)	0.26
BLOOD COUNT						
Haemoglobin, g/l		13.4 (12.5-14.5)	12.9 (11.8-14.6)	13.4 (12.5-14.7)	13.7 (12.7-14.8)	0.05
Platelets, per 10^9/uL		206 (151-286)	225 (160-292)	205.5 (161-264)	192 (152-247)	0.12
White blood cells, per 10^9/uL		8.3 (6.2-12.2)	8.1 (6.0-11.0)	6.5 (5.1-9.0)	5.9 (4.8-7.7)	0.0001(8)
Neutrophils, per 10^9/uL		6.9 (5.0-10.7)	7.0 (4.5-10.0)	4.9 (3.2-7.3)	4.0 (3.0-5.6)	0.0001(9)
Lymphocytes, per 10^9/uL		0.74 (0.57-0.99)	0.84 (0.62-1.14)	1.07 (0.65-1.37)	1.13 (0.84-1.50)	0.0001(10)
Blood urea nitrogen, mg/dl		55 (39-74)	49 (34-78)	37 (29-52)	29 (23-39)	0.0001(11)
Creatinine, mg/dl		0.91 (0.8-1.3)	1.04 (0.76-1.39)	0.92 (0.74-1.15)	0.89 (0.72-1.05)	0.007(12)
D-dimer, mg/L FEU		1990 (701-6210)	1355 (814-4025)	971 (556-1830)	579 (336-953)	0.0001(13)
Troponin T, ng/l		20 (15-44)	15.5 (9.0-31.5)	14 (9-18)	8 (6-12)	0.0001(14)
C-reactive protein, mg/l		153 (86-219)	119 (59-198)	94.2 (40.5-148)	44.2 (20-89.7)	0.0001(15)
Albumin, g/l		24 (20-37)	27 (22-59)	27 (23-34)	31 (27-34)	0.004(16)
Interleukin 6, pg/ml		167 (44-968)	309 (42-1,113)	64 (27-496)	47 (23-183)	0.003(17)
Ferritin, ug/l		1271 (499-2653)	958 (423-2184)	1513.5 (817-2824)	775 (238-1484)	0.06
COMORBIDITIES						
Cardiovascular Diseases						
Cardiovascular disease*, n (%)		38 (60.3)	59 (66.3)	56 (56.6)	51 (32.9)	<0.0001(18)
Hypertension, n (%)		30 (47.6)	42 (47.2)	47 (47.5)	39 (25.2)	<0.0001(19)

Ischaemic heart disease, n (%)		8 (12.7)	14 (15.7)	11 (11.1)	8 (5.2)	0.05
Arrythmia, n (%)		8 (12.7)	16 (18.0)	9 (9.1)	14 (9.0)	0.16
Vasculopathy, n (%)		8 (12.7)	8 (9.0)	9 (9.1)	7 (4.5)	0.19
Valvulopathy, n (%)		2 (3.2)	5 (5.6)	3 (3.0)	4 (2.6)	0.67
Heart failure, n (%)		3 (4.8)	7 (7.9)	4 (4.0)	2 (1.3)	0.07
Other						
Diabetes mellitus, n (%)		9 (14.3)	21 (23.6)	20 (20.0)	18 (11.6)	0.07
Endocrinology disease, n (%)		7 (11.1)	17 (19.1)	13 (13.1)	18 (11.7)	0.37
Neurological disease, n (%)		8 (12.7)	16 (18.0)	13 (13.1)	12 (7.7)	0.12
Immune depression, n (%)		3 (4.8)	12 (13.5)	11 (11.1)	12 (7.7)	0.24
Hypothyroidism, n (%)		2 (3.2)	9 (10.1)	9 (9.1)	10 (6.5)	0.35
Kidney disease, n (%)		5 (7.9)	8 (9.0)	7 (7.1)	8 (5.2)	0.70
Orthopaedic disease, n (%)		3 (4.8)	7 (7.9)	8 (8.1)	13 (8.4)	0.86
Gastrointestinal disease, n (%)		6 (9.5)	8 (9.0)	4 (4.0)	10 (6.5)	0.42
Severe obesity, n (%)		6 (9.5)	12 (13.5)	1 (1.0)	7 (4.5)	0.002[20]
COPD, n (%)		7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04[21]
CKD, n (%)		3 (4.8)	9 (10.1)	5 (5.1)	6 (3.9)	0.26
BPH, n (%)		7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04[22]
Active solid cancer, n (%)		2 (3.2)	7 (7.9)	4 (4.0)	7 (4.5)	0.59
Previous cancer, n (%)		4 (6.4)	4 (4.5)	2 (2.0)	8 (5.2)	0.52
Stroke, n (%)		3 (4.8)	6 (6.7)	4 (4.0)	4 (2.6)	0.44
Other neurological disease, n (%)		4 (6.4)	5 (5.6)	4 (4.0)	1 (0.7)	0.03[23]
Asthma, n (%)		1 (1.6)	3 (3.4)	4 (4.0)	5 (3.2)	0.90
CHRONIC TREATMENTS						
ACEi at admission, n (%)		12 (19.1)	13 (14.6)	24 (24.2)	9 (5.8)	<0.0001[24]
ACEi name, n (%)	Ramipril	6 (50.0)	9 (64.3)	13 (54.2)	5 (55.6)	0.90
	Enalapril	2 (16.7)	3 (21.4)	8 (33.3)	3 (33.3)	0.71
	Lisinopril	1 (8.3)	1 (7.1)	1 (4.2)	0 (0.0)	-
	Perindopril	1 (8.3)	1 (7.1)	0 (0.0)	1 (11.1)	
	Zofenpril	1 (8.3)	0 (0.0)	1 (4.2)	0 (0.0)	
	Captopril	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	Zanipril	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	
ARBs, n (%)		9 (14.3)	16 (18.0)	10 (10.1)	26 (16.8)	0.41
ARB name, n (%)	Olmesartan	6 (66.7)	6 (35.3)	2 (20.0)	11 (40.7)	0.23
	Telmisartan	1 (11.1)	3 (17.7)	3 (30.0)	4 (14.8)	0.71
	Valsartan	1 (11.1)	4 (23.5)	1 (10.0)	5 (18.5)	0.84
	Irbesartan	0 (0.0)	3 (17.7)	3 (30.0)	4 (14.8)	-
	Losartan	1 (1.1)	1 (5.9)	1 (10.0)	3 (11.1)	
ACEi or ARBs, n (%)		21 (33.3)	29 (32.6)	34 (34.3)	34 (21.9)	0.10
IN-HOSPITAL TREATMENTS						
Lopinavir/ritonavir, n (%)		40 (63.5)	50 (56.2)	64 (64.6)	87 (56.1)	0.45
Hydroxychloroquine, n (%)		51 (81.0)	74 (83.2)	89 (89.9)	120 (77.4)	0.09

Corticosteroids, n (%)	26 (41.3)	37 (41.6)	24 (24.2)	18 (11.6)	<0.0001[25]
Tocilizumab, n (%)	17 (27.0)	21 (23.6)	27 (27.3)	22 (14.2)	0.03[26]
LMWH, n (%)	48 (76.2)	66 (74.2)	62 (62.6)	73 (47.1)	<0.0001[27]
Experimental drugs, n (%)	1 (1.6)	0 (0.0)	0 (0.0)	2 (1.3)	0.74
OUTCOMES					
CPAP during hospitalization, n (%)	45 (71.4)	50 (56.2)	49 (49.5)	32 (20.7)	<0.0001[28]
Median (IQR) CPAP max PEEP	12 (10-14)	10 (10.0-12.3)	10 (10.0-12.5)	10 (10.0-12.5)	0.02[29]
Intubation, n (%)	11 (17.5)	5 (5.6)	9 (9.1)	11 (7.1)	0.06
In-hospital mortality, n (%)	35 (55.6)	43 (48.3)	16 (16.2)	10 (6.5)	<0.0001[30]
Days from admission to death	15 (6-37)	25 (7-34)	35 (24-41)	36 (30-41)	0.0001[31]

*at least one of the following 6 categories

1. Severe VS Mild p-value= 0.02; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
2. Severe VS. Mild p-value= 0.04; Severe VS. Normal p-value= 0.005; Moderate VS. Normal p-value= 0.03.
3. Severe VS. Mild p-value= 0.0002; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value= 0.0007; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
4. Severe VS. Mild p-value= 0.04; Moderate VS. Mild p-value= 0.008.
5. Severe VS. Moderate p-value= 0.002; Severe VS. Mild p-value= 0.03; Moderate VS. Normal p-value= 0.0009; Mild VS. Normal p-value= 0.03.
6. Severe VS. Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value <0.0001; Moderate VS. Normal p-value <0.0001.
7. Severe VS. Moderate p-value= 0.04; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value 0.01; Mild VS. Normal p-value 0.001.
8. Severe VS Mild p-value= 0.03; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001.
9. Severe VS Mild p-value= 0.008; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value= 0.01; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.02.
10. Severe VS Mild p-value= 0.01; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value= 0.0006.
11. Severe VS Mild p-value= 0.002; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value= 0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0006.
12. Moderate VS. Normal p-value= 0.004.
13. Severe VS Mild p-value= 0.02; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value=0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.003.
14. Severe VS Normal p-value <0.0001; Moderate VS: Normal p-value=0.001; Mild VS. Normal p-value= 0.01.
15. Severe VS Mild p-value= 0.003; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0002.

16. Severe VS. Normal p-value= 0.002.
17. Severe VS. Normal p-value= 0.02; Moderate VS: Normal p-value=0.004.
18. Severe VS. Normal p-value= 0.0002; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0002.
19. Severe VS. Normal p-value= 0.001; Moderate VS. Normal p-value= 0.0004; Mild VS. Normal p-value= 0.0003.
20. Severe VS. Moderate p-value= 0.009; Moderate VS. Mild p-value= 0.0007; Moderate VS. Normal p-value= 0.01; Mild VS. Normal p-value= 0.01.
21. Severe VS. Normal p-value= 0.02; Moderate VS. Normal p-value= 0.03.
22. Severe VS. Normal p-value= 0.02; Moderate VS. Normal p-value= 0.03.
23. NA
24. Severe VS. Normal p-value= 0.003; Moderate VS. Normal p-value= 0.02; Mild VS. Normal p-value <0.0001.
25. Severe VS Mild p-value= 0.02; Severe VS. Normal p-value <0.0001; Moderate VS Mild p-value= 0.01; Mild VS. Normal p-value= 0.008.
26. Severe VS. Normal p-value= 0.03; Mild VS. Normal p-value= 0.01.
27. Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value= 0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
28. Severe VS. Mild p-value= 0.006; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
29. Severe VS Moderate p-value= 0.005.
30. Severe VS. Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.01.
31. Severe VS Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001.

Data are expressed as frequencies or medians (inter quartile range – IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in Table 1 of the *Supplementary file*. ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure.

The proportion of patients with cardiovascular comorbidities and hypertension was significantly higher in patients with a respiratory failure if compared with that of patients with a PaO2/FiO2 >300

mmHg (p-value <0.0001). Obesity was more prevalent in patients with moderate and severe respiratory failure if compared with obesity prevalence in patients with PaO2/FiO2 ≥201 mmHg (23% VS. 5.5%; p-value= 0.002); similar differences were found for COPD (22.2% VS. 7.2%; p-value= 0.04). Chronic use of ACEi was more prevalent in patients with respiratory failure (p-value <0.0001).

The highest proportion of intubated patients was in the severe group (17.5%) (Table 2).

Impact of cardiovascular diseases and RAA system inhibitors

Overall, chronic therapy with ACEi was associated with worse PaO2/FiO2 at admission (median value 223.5 VS. 273.0; p-value = 0.004) (Table 2 of the *Supplementary file*) and higher in-hospital mortality (35.6% VS. 23.5%; p-value = 0.048) (Table 2 of the *Supplementary file* and Figure 1). Severity of respiratory failure at admission, intubation and mortality rates were not associated with ARBs therapy (Table 3 of the *Supplementary file* and Figure 1).

Patients with CVD or hypertension had significantly lower PaO2/FiO2 at admission (both p-values <0.0001), a higher proportion of respiratory failure (both p-values <0.0001), and an increased need for CPAP during the hospital stay (p-value=0.02 and 0.003, respectively) (Table 4 of the *Supplementary file* and Table 3).

Table 3. Respiratory failure and outcomes in patients with cardiovascular disease, depending on ACEi and ARBs exposure.

	Covid-19 patients (n = 412)								
	CVD No (n= 205)	CVD yes (n= 207)	p-value						
				CVD yes (n= 207)					
				ACEi No (n= 154)	ACEi Yes (n= 53)	p-value	ARBs No (n= 147)	ARBs Yes (n= 60)	p-value
PaO2/FiO2 at admission	307.5 (180-381)	206.5 (123-305)	<0.0001	203 (127-319)	228 (113-290)	0.62	201.5 (118.0-285.5)	285.5 (135-343)	0.01
RF at admission, n (%)	125 (61.0)	174 (84.1)	<0.0001	129 (83.8)	45 (84.9)	0.85	128 (87.1)	46 (76.7)	0.06
CPAP at admission, n (%)	16 (7.8)	24 (11.6)	0.19	20 (13.0)	4 (7.6)	0.29	17 (11.6)	7 (11.7)	0.98
CPAP in-hospital, n (%)	76 (37.1)	100 (48.3)	0.02	75 (48.7)	25 (47.2)	0.85	71 (48.3)	29 (48.3)	1.00
In-hospital mortality, n (%)	32 (15.6)	72 (34.8)	<0.0001	53 (34.4)	19 (35.9)	0.85	58 (39.5)	14 (23.3)	0.03
Intubation, n (%)	23 (11.2)	13 (6.3)	0.08	9 (5.8)	4 (7.6)	0.74	9 (6.1)	4 (6.7)	1.00

Data are reported as frequencies or medians (interquartile range – IQR). CVD: cardiovascular disease; ACEi: angiotensin converting enzyme inhibitor; ARBs: angiotensin receptor blockers. PaO2: arterial partial pressure of oxygen; FiO2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

In hospital mortality and respiratory failure

In-hospital mortality was 25.5%. It proportionally increased with lower PaO2/FiO2 values, being highest in the severe group (55.6%) and lowest in patients with PaO2/FiO2 >300 mmHg (6.5%; p-value <0.0001). The number of days from admission to death was lowest in the severe group and highest in patients with normal PaO2/FiO2 at admission (p-value= 0.0001) (Table 2). Age > 65 years, male sex, exposure to ACEi, having a CVD, presence of respiratory failure at admission, a PaO2/FiO2 ≤ 200 mmHg, and need for CPAP at admission were significantly associated with an increased mortality at the univariate analysis (Table 4); however, the multivariate analysis showed that the only independent risk factors were older age (Hazard rate (HR) 3.41; 95% confidence interval (CI): 2.00-5.78, p-value <0.0001), a PaO2/FiO2 ≤ 200 mmHg (HR 3.57; 95%CI: 2.20-5.77, p-value <0.0001) and the presence of respiratory failure at admission (HR 3.58; 95%CI: 1.05-12.18, p-value = 0.04) (Figure 2). Fifteen days post admission, patients with moderate to severe respiratory failure had a survival rate of 56% (Figure 2).

Table 4. Risk factors for in-hospital mortality.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >65 years	5.76 (3.46-9.60)	<0.0001	3.41 (2.00-5.78)	<0.0001
Males	1.58 (1.00-2.50)	0.049	1.17 (0.73-1.86)	0.52
Exposure to ACE inhibitors	1.68 (1.03-2.74)	0.04	1.28 (0.77-2.13)	0.34
Exposure to sartan	0.91 (0.52-1.61)	0.76		
Exposure to ACE inhibitors or sartan	1.33 (0.88-2.02)	0.17		
Cardiovascular disease	2.49 (1.63-3.79)	<0.0001	1.37 (0.88-2.13)	0.16
PaO2/FiO2 ≤200 mmHg	6.68 (4.25-10.52)	<0.0001	3.57 (2.20-5.77)	<0.0001
Presence of hARFat admission	15.08 (4.78-47.59)	<0.001	3.58 (1.05-12.18)	0.04
CPAP at admission	2.20 (1.32-3.67)	0.002	1.62 (0.96-2.72)	0.07

Multivariate Cox regression analysis that identifies risk factors for in-hospital mortality. Data are reported as hazard ratios (HR) and 95% confidence intervals (CI). ACEi: angiotensin converting enzyme inhibitor; PaO2: arterial partial pressure of oxygen; FiO2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

DISCUSSION

To the best of our knowledge, the results of the present study demonstrated for the first time the independent relationship between impaired gas exchange and clinical outcomes (mortality, intubation, and need for respiratory support).

We showed that age > 65 years, presence of respiratory failure and a PaO2/FiO2 ≤ 200 mmHg at admission were independently associated with a higher mortality rate. In fact, the mortality risk for patient without respiratory failure at admission was of 1% after 15 days from hospital admission. Conversely, survival in patients with a moderate to severe respiratory failure (PaO2/FiO2 ≤ 200 mmHg) at admission was only 56% at 15 days. The overall mortality rate in our cohort is comparable to previous reports.[5,24] However, it is higher if compared with the mortality described in other observational studies.[25,26] Richardson and coworkers reported a prevalence of respiratory failure (SpO2 <90%) of 20.4%,[25] whereas it was 72.6% in our cohort. Cheng et al. reported an in-hospital mortality as low as 11% in Wuhan, China. However, 58% of enrolled patients were not discharged from hospital at the time of the report,[26] whereas only 12% of our cohort was hospitalized at the time of writing.

Hypoxemia has been rarely considered as a risk factor for COVID-19 patients' outcome. Xie and colleagues showed that patients with SpO2 <90% had 47 times more the probability to die when compared with patients with SpO2 >90%.[27] However, in patients with COVID-19 associated pneumonia, low PaO2 values can be associated with satisfactory SpO2, hiding hypoxia, which might lead to an underestimation of the severity of the disease and in a treatment delay.[28] On this basis, clinicians should not rely solely on SpO2 values, especially when evaluating patients in which symptoms had lasted for 10-12 days before their presentation to the emergency department.[29] The ratio between PaO2 and FiO2 has been demonstrated to be a reliable tool to assess severity and stratify mortality risk.[17] When compared with the ARDS Berlin's definition, our respiratory failure classes had a slightly higher mortality with PaO2/FiO2 <200 mmHg (severe 55% VS. 45% and moderate 48% VS. 35%). This should probably depend on the cohort heterogeneity and in, in our case, the absence of 5 cmH2O of PEEP used in the Berlin definition to grade severity of ARDS. Another issue is the low number of patients with severe respiratory failure at admission who

underwent intubation (n= 11). This finding can be justified by the higher chance of DNI orders in patients with severe respiratory failure, secondary to the median age and to the higher prevalence of CVD.[5] However, the absence of respiratory failure at admission or a mild hypoxia did not preclude the chance of in-hospital death or intubation. Sign of respiratory distress and worsening gas exchange should be closely monitored, as a sudden and rapidly evolving disease can involve patients in stable conditions.[29, 30]

CVD and hypertension are the most frequently observed comorbidities in patients with COVID-19 and are associated with severe disease.[31, 32] A debate was focused on the negative effects of ACEi and ARBs due to the role of the ACE2 receptor in viral-host dynamics.[32] However, several studies ruled out the increased risk of COVID-19 infection and the link between disease severity and antihypertensive treatment.[28,31,33] Our cohort was characterized by a high prevalence of CVD (50.2%), which was associated with a significantly higher mortality compared with patients without CVD. However, mortality did not change in patients chronically exposed to ACEi and ARBs. ACEi was associated with a significantly higher mortality, potentially explained by the higher disease severity of at admission of patients taking ACEi. Indeed, neither CVD, nor hypertension, nor the exposure to antihypertensive medications were independently associated with decreased survival.

Study limitations

The initial gas exchange assessment was not homogeneously conducted in all patients at admission (only 30.3% of patients were in room air conditions). This might have underestimated the severity of respiratory failure, especially in patients treated with CPAP at admission. At the time of writing, 12% of patients were still hospitalized, biasing mortality and length of stay estimates. Furthermore, a selection bias could be hypothesized, being the participating centres hub for severe patients transferred from peripheral hospitals. The local standard operating procedures, criteria for ICU admittance or management with CPAP/NIV implemented in Italy could differ in other settings, limiting the inference of our findings.

CONCLUSIONS

The severity of respiratory failure assessed with the PaO2/FiO2 ratio is significantly associated with intubation rate, need for respiratory support, and in-hospital mortality. Age, respiratory failure and PaO2/FiO2 value at admission are independently associated with in-hospital mortality. Although the findings of the present study need to be confirmed in larger cohorts, they suggest that severity of hypoxemia can be useful to triage patients with COVID-19 pneumonia and identify patients at higher risk of unfavourable outcomes.

DATA AVAILABILITY

P.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the decision to submit for publication. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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COMPETING INTERESTS STATEMENT

The Authors have no competing interests to declare in regard with the present study.

AUTHORS' CONTRIBUTIONS

P.S. and D.R. conceived the study and contributed to data collection, analysis and interpretation. G.S. performed the data analysis and contributed to study design and interpretation. L.S. performed the analysis and contributed to data interpretation. P.M., C.C., G.D.F., M.R., E.F., S.P., F.G., M.D.M., G.N., V.V. AND F.T. contributed to data collection and interpretation. P.S., D. R., G.S. and L.S. drafted and revised the manuscript. All authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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The corresponding author here confirms that he has listed everyone who contributed significantly to the work.

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FIGURES' LEGENDS

Figure 1. Survival curves based on ACEi or ARBs exposure

Survival in patients hospitalized with COVID-19 pneumonia (n = 412) based on the chronic exposure to ACEi (angiotensin converting enzyme inhibitors, upper panel) or angiotensin receptor blockers (ARBs, lower panel).

Figure 2. Survival in patients hospitalized for COVID-19 based on age and severity of respiratory failure.

Hazard ratio for survival in patients hospitalized with COVID-19 pneumonia stratified by age (> or ≤ 65 years, Panel A), severity of respiratory failure at admission (PaO2/FiO2 ratio ≤ 200 mmHg and > 200 mmHg, Panel B) and presence of respiratory failure at admission (Panel C). Note that 15 days post admission, patients with moderate to severe respiratory failure had a survival rate of about 56%, while patients without respiratory failure (Panel C) had a survival rate of 99%.
PaO2/FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio.

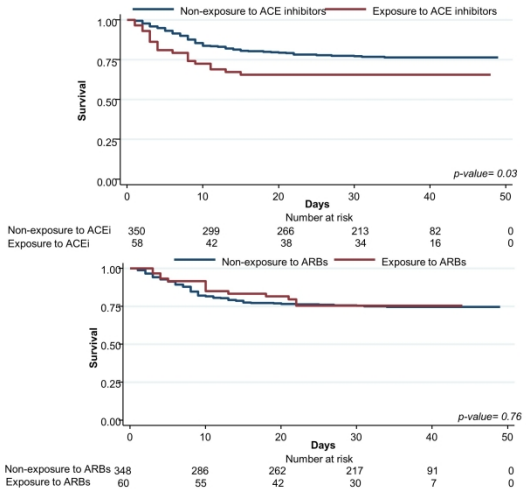

Figure 1. Survival curves based on ACEi or ARBs exposure
Survival in patients hospitalized with COVID-19 pneumonia (n = 412) based on the chronic exposure to ACEi (angiotensin converting enzyme inhibitors, upper panel) or angiotensin receptor blockers (ARBs, lower panel).

338x190mm (300 x 300 DPI)

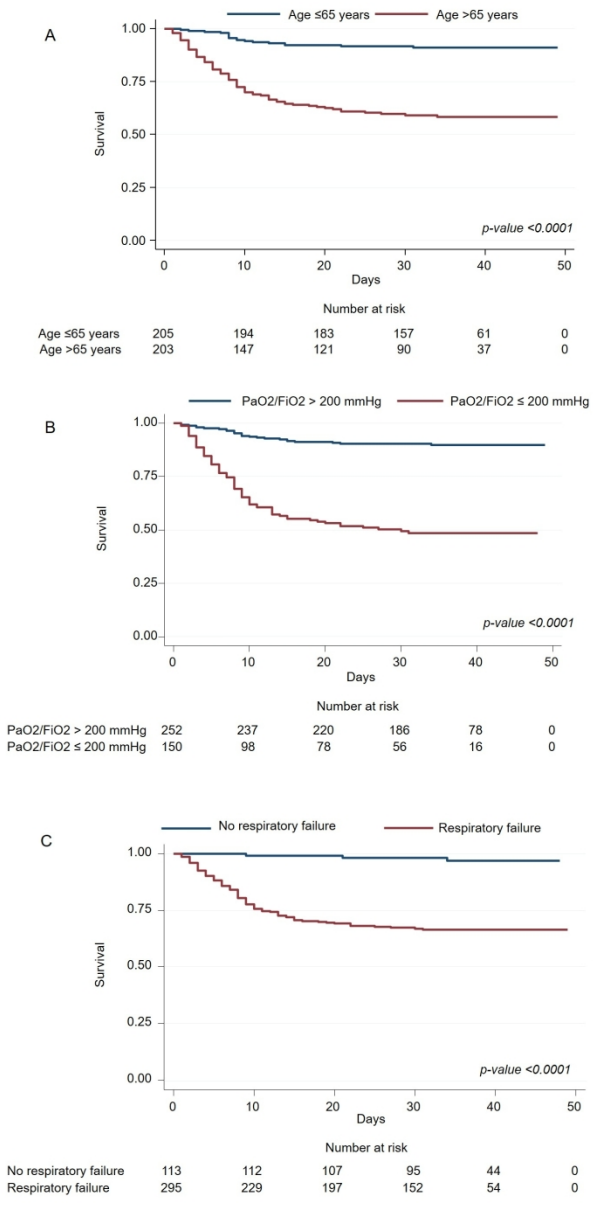

Figure 2. Survival in patients hospitalized for COVID-19 based on age and severity of respiratory failure. Hazard ratio for survival in patients hospitalized with COVID-19 pneumonia stratified by age (> or ≤ 65 years, Panel A), severity of respiratory failure at admission (PaO2/FiO2 ratio ≤ 200 mmHg and > 200 mmHg, Panel B) and presence of respiratory failure at admission (Panel C). Note that 15 days post admission, patients with moderate to severe respiratory failure had a survival rate of about 56%, while patients without respiratory failure (Panel C) had a survival rate of 99%. PaO2/FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio.

232x466mm (150 x 150 DPI)

SUPPLEMENTAL MATERIAL

TITLE: SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY.

Participating centers

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The study protocol is available at: ClinicalTrials.gov: NCT04307459

Definition of immunocompromission

Immunocompromission was defined as the presence of ≥1 of the following risk factors:[1]

1. Acquired Immuno-Deficiency Syndrome (AIDS), defined either as human immunodeficiency virus infection with CD4+ lymphocyte count <200/μL or by the occurrence of AIDS-defining conditions;
2. aplastic anemia;
3. asplenia;
4. hematological cancer, defined as lymphoma, acute or chronic leukemia, or multiple myeloma;
5. chemotherapy during the last 3 months;

6. neutropenia, defined as a neutrophil count <500/dL at complete blood cell count;
7. biological drug use (including trastuzumab and therapies for autoimmune diseases, e.g., anti–tumor necrosis factor α, prescribed during ≥6 months before hospital admission);
8. lung transplantation;
9. chronic steroid use (>10 mg/d of prednisone or equivalent ≥3 months before hospital admission);
10. lung cancer with either neutropenia or chemotherapy;
11. other solid tumor with either neutropenia or chemotherapy;
12. other immunocompromise (any immunocompromised state, including congenital/genetic immunocompromised and immunosuppressive therapy due to hematological cancer/solid organ transplantation other than lung).

Criteria for hospitalization

Hospitalization criteria were based on the standard operating procedures created for the management of patients with suspected Covid-19,[2, 3] and on the latest international recommendations.[4, 5] Criteria included any of the following: 1) the presence of respiratory failure at admission (a PaO2 <60 mmHg while breathing room air or a PaO2/FiO2 ratio <300 mmHg); 2) age >65 years old with one or more comorbidities, pulmonary infiltrates at the chest X-ray or Ct scan and respiratory distress (a respiratory rate ≥ 30 breaths/minute and dyspnea); 3) pulmonary infiltrates and persistence of respiratory symptoms (cough, chest tightness, dyspnea at rest or during effort, fever) for more than 10 days; 4) pulmonary infiltrates with evidence of oxygen desaturation (drop in SpO2 of more than 4 units from resting value) while walking for 3 minutes; 5) hemodynamic instability, sepsis or shock; 6) sepsis and septic shock; 7) pulmonary infiltrates associated with confusion or a Glasgow Coma Scale <15; 8) inability to cope with outpatient therapy due to psychosocial or such as inability to maintain oral intake, history of substance abuse, cognitive impairment, severe comorbid illnesses, and impaired functional status.[5]

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Supplemental Table 1. Complete list of comorbidities observed in the study sample.

COMORBIDITIES	
Hypertension, n (%)	160 (38.8)
Ischaemic heart disease, n (%)	43 (10.4)
Arrythmia, n (%)	49 (11.9)
Vasculopathy, n (%)	32 (7.8)
Valvulopathy, n (%)	15 (3.6)
Heart failure, n (%)	17 (4.1)
Cardiovascular disease*, n (%)	207 (50.2)
Diabetes mellitus, n (%)	69 (16.8)
Severe obesity, n (%)	26 (6.3)
COPD, n (%)	25 (6.1)
Obstructive sleep apnoea syndrome, n (%)	5 (1.2)
Asthma, n (%)	13 (3.2)
Interstitial lung disease, n (%)	1 (0.2)
Active solid cancer, n (%)	20 (4.9)
Active haematological tumour, n (%)	7 (1.7)
Previous cancer, n (%)	18 (4.4)
Anaemia, n (%)	8 (1.9)
Immune depression, n (%)	39 (9.5)
Psychiatric disease, n (%)	12 (2.9)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Kidney disease, n (%)	31 (7.5)
Gastrointestinal disease, n (%)	28 (6.8)
MRGE, n (%)	12 (2.9)
Rheumatology, n (%)	4 (1.0)
Orthopaedic disease, n (%)	31 (7.5)
BPH, n (%)	25 (6.1)
Infectious, n (%)	7 (1.7)
Eye disease, n (%)	9 (2.2)
ORL, n (%)	4 (1.0)
Haematological disease, n (%)	8 (1.9)
Gynaecological disease, n (%)	9 (2.2)
Depression, n (%)	9 (2.2)
Others psychiatric disease, n (%)	5 (1.2)
Hypothyroidism, n (%)	32 (7.8)
Hyperuricemia, n (%)	4 (1.0)
Osteoporosis, n (%)	7 (1.7)
Others endocrinological disease, n (%)	8 (1.9)
Stroke, n (%)	17 (4.1)
Mental disability, n (%)	5 (1.2)
Alzheimer, n (%)	5 (1.2)
Dementia, n (%)	7 (1.7)

Epilepsy, n (%)	8 (1.9)
Others neurological disease, n (%)	14 (3.4)
CKD, n (%)	25 (6.1)
Kidney stones, n (%)	7 (1.7)
Others renal disease, n (%)	7 (1.7)
Cholecystectomy, n (%)	9 (2.2)
Appendectomy, n (%)	9 (2.2)
Gastric/Duodenal ulcer, n (%)	6 (1.5)
Chronic Hepatitis-C, n (%)	6 (1.5)
Others gastro, n (%)	18 (4.4)
Prosthetics, n (%)	12 (2.9)
Hernia, n (%)	14 (3.4)
Others surgery, n (%)	8 (1.9)
Hysterectomy, n (%)	7 (1.7)
Others gynaecology, n (%)	0 (0.0)

BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; ORL: otolaryngology.

Supplemental Table 2. Respiratory failure and outcomes in patients exposed and not exposed to angiotensin converting enzyme inhibitors

	Not-exposure to ACE inhibitors (n= 353)	Exposure to ACE inhibitors (n= 59)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	273 (148.0-346.5)	223.5 (113-290)	0.004
Presence of respiratory failure at admission, n (%)	250 (70.8)	49 (83.1)	0.05
Need for CPAP at admission, n (%)	34 (9.6)	6 (10.2)	0.90
Need for CPAP during the hospital stay, n (%)	148 (41.9)	28 (47.5)	0.43
In-hospital mortality, n (%)	83 (23.5)	21 (35.6)	0.048
Need for intubation, n (%)	31 (8.8)	5 (8.5)	0.94

ACEi: angiotensin converting enzyme inhibitors; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 3. Respiratory failure severity and outcomes in patients exposed and not exposed to angiotensin receptor blockers

	Non-exposure to ARBs (n = 351)	Exposure to ARBs (n= 61)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	262 (140-341)	289 (140-343)	0.98
Presence of respiratory failure at admission, n (%)	252 (71.8)	47 (77.1)	0.40
Need for CPAP at admission, n (%)	32 (9.1)	8 (13.1)	0.33
Need for CPAP during the hospital stay, n (%)	146 (41.6)	30 (49.2)	0.27
In-hospital mortality, n (%)	90 (25.6)	14 (23.0)	0.66
Need for intubation, n (%)	32 (9.1)	4 (6.6)	0.63

ARBs: angiotensin receptor blockers; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 4. Severity of respiratory failure and outcomes in patients with hypertension compared with patients without hypertension.

	Hypertension (n = 160)	No-hypertension (n= 252)	p-value	No-hypertension (n= 252)			
				Without CVD (n=205)	p-value*	With CVD (n= 47)	p-value*
PaO_2/FiO_2 at admission, mmHg	214.5 (120.0-300.0)	291.5 (153.5-362.0)	<0.0001	307.5 (180-381)	<0.0001	184 (126-310)	0.65
Respiratory failure at admission, n (%)	135 (84.4)	164 (65.1)	<0.0001	125 (61.0)	<0.0001	39 (83.0)	0.82
CPAP at admission, n (%)	18 (11.3)	22 (8.7)	0.40	16 (7.8)	0.26	6 (18.8)	0.78
CPAP in-hospital, n (%)	76 (47.5)	100 (39.7)	0.12	76 (37.1)	0.045	24 (51.2)	0.67
In-hospital mortality, n (%)	53 (33.1)	51 (20.2)	0.003	32 (15.6)	<0.0001	19 (40.4)	0.36
Intubation, n (%)	10 (6.3)	26 (10.3)	0.15	23 (11.2)	0.10	3 (6.4)	0.97

A sensitivity analysis has been performed excluding patients with cardiovascular diseases from patients without hypertension. PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

* VS. patients with hypertension

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract DONE – page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. DONE – page 3 and 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. DONE – page 6
Objectives	3	State specific objectives, including any prespecified hypotheses. DONE – page 6
Methods		
Study design	4	Present key elements of study design early in the paper. DONE – page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. DONE- page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. DONE- page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed. N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. DONE - page 7 and 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. DONE – page 7 and 8
Bias	9	Describe any efforts to address potential sources of bias. DONE – page 7 and 8
Study size	10	Explain how the study size was arrived at DONE - page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. DONE page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. DONE – page 9
		(*b*) Describe any methods used to examine subgroups and interactions. DONE – page 9
		(*c*) Explain how missing data were addressed. DONE, table 1 (pages 10-12)
		(*d*) If applicable, explain how loss to follow-up was addressed. N/A
		(*e*) Describe any sensitivity analyses. N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. DONE – Page 9
		(b) Give reasons for non-participation at each stage. N/A
		(c) Consider use of a flow diagram. N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. DONE - page 10-12
		(b) Indicate number of participants with missing data for each variable of interest - DONE - page 10-12
		(c) Summarise follow-up time (eg, average and total amount). DONE – page 16-16
Outcome data	15*	Report numbers of outcome events or summary measures over time. DONE – page 15-16 and Figure 1

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. DONE – page 20
		(*b*) Report category boundaries when continuous variables were categorized. DONE – page 20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. DONE – Page 18 and Supplementary material Tables 2 to 4
Discussion		
Key results	18	Summarise key results with reference to study objectives. DONE – Page 21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. DONE – Page 22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. DONE – Page 21-22
Generalisability	21	Discuss the generalisability (external validity) of the study results. DONE – Page 22
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. DONE – Page 23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	COVID-19, Respiratory physiology < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), VIROLOGY, Respiratory infections < THORACIC MEDICINE

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TITLE: SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY.

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ABSTRACT

Objectives: Coronavirus Disease 2019 (COVID-19) causes lung parenchymal and endothelial damage that lead to hypoxic acute respiratory failure (hARF). The influence of hARF severity on patients' outcomes is still poorly understood.

Design: observational, prospective, multicenter study.

Setting: three academic hospitals in Milan (Italy) involving three respiratory high dependency units and three general wards.

Participants: consecutive adult hospitalized patients with a virologically-confirmed diagnosis of COVID-19. Patients with <18 years old or unable to provide informed consent were excluded.

Interventions: anthropometrical, clinical characteristics and blood biomarkers were assessed within the first 24 hours from admission. hARF was graded as follows: severe (partial pressure of oxygen to fraction of inspired oxygen ratio [PaO2/FiO2] <100 mmHg); moderate (PaO2/FiO2 101-200 mmHg); mild (PaO2/FiO2 201-300 mmHg) and normal (PaO2/FiO2 >300 mmHg).

Primary and secondary outcome measures: the primary outcome was the assessment of clinical characteristics and in-hospital mortality based on the severity of respiratory failure. Secondary outcomes were intubation rate and application of continuous positive airway pressure (helmet CPAP) during hospital stay.

Results: 412 patients were enrolled (280 males, 68%). Median (interquartile range – IQR) age was 66 (55-76) years with a PaO2/FiO2 at admission of 262 (140-343) mmHg. 50.2% had a cardiovascular disease (CVD). Prevalence of mild, moderate and severe hRF was 24.4%, 21.9% and 15.5%, respectively. In-hospital mortality proportionally increased with increasing impairment of gas exchange (p-value<0.001). The only independent risk factors for mortality were age ≥65 years (Hazard rate (HR) 3.41; 95% confidence interval (CI): 2.00-5.78, p-value<0.0001), PaO2/FiO2 ratio≤200 mmHg (HR 3.57; 95%CI: 2.20-5.77, p-value<0.0001) and respiratory failure at admission (HR 3.58; 95%CI: 1.05-12.18, p-value=0.04).

Conclusions: A moderate--severe impairment in PaO2/FiO2 was independently associated with a threefold increase in risk of in-hospital mortality. Severity of respiratory failure is useful to identify patients at higher risk of mortality.

Trial registration: NCT04307459

STRENGTHS AND LIMITATIONS (LIMITED TO METHODS)

- This was a multicentre, prospective study
- The study has enrolled a conspicuous of well characterized patients hospitalized with COVID-19 pneumonia
- A selection bias may be due to the high number of severe patients due to the Hub characteristics of the participating centres
- Not all patients were evaluated in room air conditions at admittance, thus potentially underestimating the severity of the study sample

INTRODUCTION

The severe acute respiratory syndrome Coronavirus type 2 (SARS-CoV-2) and the related Coronavirus Disease 2019 (COVID-19) has caused a pandemic and ~860,000 deaths worldwide.[1] The clinical spectrum can range from mild symptoms (e.g., fever and malaise) to severe hypoxic respiratory failure, sepsis, multi-organ involvement, and death. The infection appears to induce an inflammatory reaction with pulmonary infiltrates generating hypoxemia secondary to intra-parenchymal shunt and ventilation/perfusion mismatch, favored by endothelial damage and dysfunction, and altered regulation of perfusion and associated with macro and/or microembolism.[2,3] So far, risk factors such as older age,[4-6] severity of clinical presentation [4-7], increased D-dimer values,[4] cardiovascular disease (CVD),[4,5] and hypertension [5-8] have been associated with unfavorable outcomes.

It has been proposed that clinical severity of COVID-19 should depend on the presence of any of the following criteria: a partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio <300 mmHg, a respiratory rate >30 per minute, and a peripheral oxygen saturation (SpO2) <93%.[4, 9-12] Several consensus statements recommend different PaO2 and SpO2 thresholds to prescribe continuous positive airway pressure (CPAP),[13-15] non-invasive ventilation, or intubation.[16] Data on the association between severity of respiratory failure at admission and patients' outcomes are still limited.

The aim of the present study was to assess the clinical characteristics of COVID-19 patients based on the severity of respiratory failure, and to explore the relationship between the degree of gas exchange impairment and clinical outcomes (CPAP initiation and mortality).

METHODS

An observational, prospective, multicenter study was conducted in three academic hospitals in Milan (Italy) from March 7 to May 7, 2020, involving three respiratory high dependency units and three general wards. A detailed list of participating centers is reported in the *Supplementary file*. The study protocol (ClinicalTrials.gov: NCT04307459), designed following the amended Declaration of Helsinki (2013), was approved by the local ethical committee (Comitato Etico Milano Area I; 17263/2020) and

all recruited patients gave written informed consent. The authors received no specific funding for this work.

Patient and Public Involvement

Participants were not involved in the design and conduct of the research, interpretation of results and writing of the manuscript. The results of the study will be shared with local patients' organizations by social media and summary reports on organizations' websites.

Patients

Adult hospitalized patients with a virologically-confirmed diagnosis of SARS-CoV-2 infection were considered eligible for study enrolment. Patients with <18 years old or unable to provide informed consent were excluded from the study. Hospitalization criteria are reported in the *Supplementary file.*

Procedures

Anthropometrical and clinical characteristics were collected at admission. The PaO2/FiO2 ratio was calculated from the first available arterial blood gas analysis performed in the emergency department. PaO2/FiO2 thresholds to grade severity of respiratory failure were taken from the Acute Respiratory Distress Syndrome (ARDS) Berlin definition, and were:[17] normal (PaO2/FiO2 >300 mmHg); mild (PaO2/FiO2 201-300 mmHg); moderate (PaO2/FiO2 101-200 mmHg); severe (PaO2/FiO2 ≤100 mmHg). Blood count and biochemistry parameters were assessed during the first 24 hours after hospital admission.

Outcomes

The primary outcome was the description of patients' clinical characteristics at admission and the assessment of in-hospital mortality based on the severity of respiratory failure.

Secondary outcomes were the assessment of intubation rate and application of CPAP during the hospital stay.

Study definitions

SARS-CoV-2 infection and co-infections

The COVID-19 diagnosis was based on a positive nasopharyngeal swab collected in the emergency department. *SARS-CoV-2* infection was proved by means of reverse transcriptase polymerase chain reaction (RT-PCR). In case a first swab was negative, and the clinical picture was highly suggestive for COVID-19, the swab was repeated. Co-infection with *Influenza virus* A and B, A*denovirus*, *human Rhinovirus, Respiratory Syncytial virus*, *human Metapneumovirus* were also investigated and analyzed by means of RT-PCR or rapid influenza diagnostic tests (RIDTs).[18] Microbiological testing for bacteria and fungi in blood, upper and lower airway tract, sputum and urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed according to standard operating protocols.

Management of respiratory failure

Helmet CPAP was the only non invasive respiratory support used in patients with confirmed or suspected COVID-19 pneumonia not responsive to oxygen masks in order to reduce the viral exposure of the healthcare workers in rooms without negative pressure.[19] Patients with a PaO2/FiO2 ratio <300 mmHg in room air were administered oxygen with nasal cannulae to reach a SpO2 of 94% or PaO2 >60 mmHg; in case of unsuccessful intervention within 30 minutes, patients were put on reservoir masks with 90-100% FiO2 or helmet CPAP was initiated with PEEP up to 12 cmH2O based on the respiratory distress and comorbidities following standard operating procedures as previously described.[14] CPAP failure after two hours with the maximal tolerable PEEP and a FiO2 of 100% was considered in case of: a) persistence of PaO2/FiO2<300 mmHg; b) hemodynamic instability (systolic blood pressure <90 mmHg despite adequate fluid support) or altered consciousness; d) respiratory distress, fatigue and/or a respiratory rate >30 bpm.[20] Patients that fulfilled CPAP failure criteria were evaluated by an ICU physician for potential intubation. A do not intubate (DNI) order was established by the treating attending physician following a multidisciplinary discussion with the unit staff and the ICU and based on patient's age, comorbidities and clinical status.

In hospital treatment

Unless contraindicated, patients received hydroxychloroquine and lopinavir/ritonavir following local standard and Italian guidelines.[21,22] In patients with severe pneumonia, methylprednisolone was given at a maximal dose of 1 mg/Kg according to the ATS/IDSA guidelines [23] and local standard operating procedures. Criteria for methylprednisolone initiation included age <80 years, PaO2/FiO2 <250 mmHg, bilateral infiltrates at the chest x-ray or CT scan, a C-reactive protein>100 mg/l, and/or a diagnosis of ARDS according to the Berlin definition [17]. Immunomodulation with off-label tocilizumab at a dosage of 8 mg/Kg body weight was administered in patients with signs of hyper-inflammatory syndrome and elevated IL-6.[21] Unless contraindicated, patients received prophylactic low molecular weight heparin (LMWH) or were switched to therapeutic LMWH dosage if already on chronic anticoagulant therapy. Patients with signs of deep vein thrombosis, pulmonary embolism or D-dimer values >5,000 received a therapeutic dose of LMWH.

Statistical Analysis

Qualitative variables were summarized with absolute and relative (percentage) frequencies. Parametric and non-parametric quantitative variables were described with means (standard deviations, SD) and medians (interquartile ranges, IQR), respectively. Chi-squared or Fisher exact test were used to compare qualitative variables, whereas Student t test or Mann-Whitney, ANOVA or Kruskall-Wallis, corrected with Sidak adjustment, were used to compare quantitative variables with normal or non-normal distribution, respectively. Cox proportional hazard regression analysis was performed to assess the relationship between clinical outcomes and independent variables. Kaplan-Meier survival curves were plotted to show differences for the outcome mortality, considering the confounding variables age, respiratory failure, PaO2/FiO2 and antihypertensive treatment; log-rank test was computed to assess the presence of any statistically significant differences. A two-tailed p-value less than 0.05 was considered statistically significant. All statistical computations were performed with the statistical software STATA version 16 (StatsCorp, Texas, USA).

RESULTS

Clinical characteristics of the whole sample size

A total of 412 patients were enrolled (280 males, 68%) (Table 1). The median (interquartile range – IQR) age at admission was 66 (55-76) years, and 54.6% of patients were ≥ 65 years old. 61.8% of patients had a PaO2/FiO2 <300 mmHg, with a median (IQR) PaO2/FiO2 of 262 (140-343) mmHg. 24.4% had mild, 21.9% moderate, and 15.5% severe respiratory failure. CPAP was prescribed in the emergency department in 9.7% of cases, whereas only 3 patients were immediately intubated. Median (IQR) white blood cell (WBC) count was 6.7 (5.1-9.4) per 10^9/μL, 10.9% had leukopenia, and 45.9% had lymphocytopenia. Median (IQR) D-dimer values were 890.5 (470-2,157) mg/L fibrinogen-equivalent units (FEU), and 34% had a D-dimer >1,000 mg/L FEU (Table 1).

Table 1. Characteristics and outcomes of patients at admission.

		Covid-19 patients (n= 412)
Age at admission, years		66 (55-76)
Males, n (%)		280 (68.0)
SARS-COV-2 positive swab, n (%)		412 (100.0)
PaO2/FiO2 at admission, mmHg		262 (140-343)
PaO2/FiO2 severity, n (%)	≤ 100, mmHg	64 (15.5)
	101-200, mmHg	90 (21.9)
	201-300, mmHg	101 (24.4)
	>300, mmHg	157 (38.2)
Respiratory support at admission, n (%)	Room air	125 (30.3)
	Nasal cannulae	93 (22.6)
	Venturi mask	78 (18.9)
	Reservoir mask	68 (16.5)
	CPAP	40 (9.7)
	NIV	5 (1.2)
	IMV	3 (0.7)
BLOOD COUNT and BIOCHEMISTRY		
Haemoglobin, g/l (n= 401)		13.4 (12.4-14.6)
Platelets, per 10^9/uL (n=401)		203 (156-270)
Platelets <100 per 10^9/uL, n (%) (n=401)		17 (4.1)
White blood cells, per 10^9/uL (n=401)		6.7 (5.1-9.4)

White blood cells < 4.0 per 10^9/uL, n (%) (n=401)	45 (10.9)
Neutrophils, per 10^9/uL (n=401)	5.1 (3.3-8.1)
Neutrophils <1.5 per 10^9/uL, n (%) (n=401)	7 (1.7)
Lymphocytes, per 10^9/uL (n=401)	0.98 (0.67-1.33)
Lymphocytes < 1.0 per 10^9/uL, n (%) (n=401)	189 (45.9)
Lymphocytes < 0.5 per 10^9/uL, n (%) (n=401)	44 (10.7)
Blood urea nitrogen, mg/dl (n=372)	37.5 (27-56)
Creatinine, mg/dl (n=401)	0.93 (0.75-1.19)
Creatinine >1.2 mg/dl, n (%) (n=401)	95 (23.1)
D-dimer, mg/L FEU (n=400)	890.5 (470-2,157)
D-dimer ≥ 1,000 mg/L FEU, n (%) (n=195)	140 (34.0)
Troponin T, ng/l (n=125)	13 (7.0-22.4)
C-reactive protein, mg/l (n=400)	84.6 (36.2-158.0)
Albumin, g/l (n=151)	28 (23-35)
Interleukin 6 pg/ml (n=83)	86 (31-693)
Ferritin, ug/l (n=145)	1063 (408-2145)
COMORBIDITIES	
Cardiovascular Diseases	
Any cardiovascular disease*, n (%)	207 (50.2)
Hypertension, n (%)	160 (38.8)
Arrhythmia, n (%)	49 (11.9)
Ischaemic heart disease, n (%)	43 (10.4)
Vasculopathy, n (%)	32 (7.8)
Heart failure, n (%)	17 (4.1)
Valvulopathy, n (%)	15 (3.6)
Other	
Diabetes mellitus, n (%)	69 (16.8)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Immune depression, n (%)	39 (9.5)
Hypothyroidism, n (%)	32 (7.8)

Kidney disease, n (%)		31 (7.5)
Orthopaedic disease, n (%)		31 (7.5)
Gastrointestinal disease, n (%)		28 (6.8)
Severe obesity, n (%)		26 (6.3)
COPD, n (%)		25 (6.1)
CKD, n (%)		25 (6.1)
BPH, n (%)		25 (6.1)
Active solid cancer, n (%)		20 (4.9)
Previous cancer, n (%)		18 (4.4)
Stroke, n (%)		17 (4.1)
Other neurological disease, n (%)		14 (3.4)
Asthma, n (%)		13 (3.2)
CHRONIC TREATMENTS		
ACEi at admission, n (%)		59 (14.3)
ACEi name, n (%)	Ramipril	34 (56.7)
	Enalapril	16 (26.7)
	Lisinopril	3 (5.0)
	Perindopril	3 (5.0)
	Zofenpril	2 (3.3)
	Captopril	1 (1.7)
	Zanipril	1 (1.7)
ARBs, n (%)		61 (14.8)
ARB name, n (%)	Olmesartan	25 (39.7)
	Telmisartan	11 (17.5)
	Valsartan	11 (17.5)
	Irbersartan	10 (15.9)
	Losartan	6 (9.5)
ACEi or ARBs, n (%)		119 (28.9)
IN-HOSPITAL TREATMENTS		
Hydroxychloroquine, n (%)		336 (81.6)
Lopinavir/ritonavir, n (%)		242 (58.7)
Corticosteroids, n (%)		105 (25.5)
LMWH, n (%)		249 (60.4)
Tocilizumab, n (%)		88 (21.6)
Experimental drugs, n (%)**		3 (0.7)
OUTCOMES		
CPAP during hospitalization, n (%)		176 (42.7)
CPAP max PEEP		10 (10.0-12.5)
Discharge at home, n (%)		180 (43.7)
Discharge to other facility, n (%)		41 (10.0)
In-hospital mortality, n (%)		105 (25.5)
Intubation, n (%)		36 (8.7)
Still hospitalized, n (%)		50 (12.1)

Demographic, clinical characteristics, respiratory failure parameters at admission, and clinical outcomes in 412 patients hospitalized with Covid-19 pneumonia. Data are expressed as frequencies or medians (inter quartile range – IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in Table 1 of the *Supplementary file.* Missing values, if present, are reported next to each variable. ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; FEU: fibrinogen-equivalent units; LMWH: low molecular weight heparin; NIV: non invasive ventilation; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure; RF: respiratory failure. *at least one of the following 6 categories; **Remdesivir

Half of the patients (50.2%) showed cardiovascular comorbidities, with hypertension being the most prevalent (38.8%). Diabetes and chronic kidney disease were observed in 16.8% and 13.6% of the cases, respectively. Chronic obstructive pulmonary disease (COPD) and asthma accounted for the 6.1% and 3.2% of the study sample. A complete list of observed comorbidities is reported in Table 1 of the Supplementary file.

The most frequently administered therapy was hydroxychloroquine (81.6%), whereas corticosteroids and tocilizumab were prescribed in 25.5% and 21.6% of the patients, respectively.

During the hospital stay, 42.7% were exposed to CPAP, 8.7% underwent mechanical ventilation and were transferred to the ICU.

Characteristics based on severity of respiratory failure

The cohort was divided in four groups based on the severity of respiratory failure (Table 2). Advanced age and male were more prevalent in patients with severe respiratory failure (p-value= 0.0001 and 0.02, respectively).

WBC, neutrophils, c-reactive protein, and D-dimer values were higher in severe cases (all p-values = 0.0001). Impaired gas exchange was associated with a decreased lymphocyte counts, ranging from a median (IQR) value of 1.13 (0.84-1.50) per 10^9/μL in patients with PaO2/FiO2 >300 mmHg to 0.74 (0.57-0.99) per 10^9/μL in patients with severe respiratory failure (p-value= 0.0001).

Table 2. Patients' characteristics and outcomes depending on the severity of respiratory failure.

VARIABLES		Severe (P/F ≤100 mmHg) (n= 63)	Moderate (P/F 101-200 mmHg) (n= 89)	Mild (P/F 201-300 mmHg) (n= 99)	Normal (P/F >300 mmHg) (n= 155)	p-value
Age at admission, years		75 (64-81)	72 (63-81)	67 (57-76)	58 (48-70)	0.0001(1)
Males, n (%)		51 (81.0)	67 (75.3)	65 (65.7)	95 (61.3)	0.02(2)
Respiratory support at admission, n (%)	Room air	1 (1.6)	5 (5.6)	23 (23.2)	93 (60.0)	<0.0001(3)
	Nasal cannulae	11 (17.5)	14 (15.7)	32 (32.3)	35 (22.6)	0.03(4)
	Venturi mask	6 (9.5)	27 (30.3)	23 (23.2)	20 (12.9)	0.001(5)
	Reservoir mask	29 (46.0)	31 (34.8)	5 (5.1)	3 (1.9)	<0.0001(6)
	CPAP	14 (22.2)	9 (10.1)	13 (13.1)	4 (2.6)	<0.0001(7)
	NIV	1 (1.6)	2 (2.3)	2 (2.0)	0 (0.0)	0.16
	IMV	1 (1.6)	1 (1.1)	1 (1.0)	0 (0.0)	0.26
BLOOD COUNT						
Haemoglobin, g/l		13.4 (12.5-14.5)	12.9 (11.8-14.6)	13.4 (12.5-14.7)	13.7 (12.7-14.8)	0.05
Platelets, per 10^9/uL		206 (151-286)	225 (160-292)	205.5 (161-264)	192 (152-247)	0.12
White blood cells, per 10^9/uL		8.3 (6.2-12.2)	8.1 (6.0-11.0)	6.5 (5.1-9.0)	5.9 (4.8-7.7)	0.0001(8)
Neutrophils, per 10^9/uL		6.9 (5.0-10.7)	7.0 (4.5-10.0)	4.9 (3.2-7.3)	4.0 (3.0-5.6)	0.0001(9)
Lymphocytes, per 10^9/uL		0.74 (0.57-0.99)	0.84 (0.62-1.14)	1.07 (0.65-1.37)	1.13 (0.84-1.50)	0.0001(10)
Blood urea nitrogen, mg/dl		55 (39-74)	49 (34-78)	37 (29-52)	29 (23-39)	0.0001(11)
Creatinine, mg/dl		0.91 (0.8-1.3)	1.04 (0.76-1.39)	0.92 (0.74-1.15)	0.89 (0.72-1.05)	0.007(12)
D-dimer, mg/L FEU		1990 (701-6210)	1355 (814-4025)	971 (556-1830)	579 (336-953)	0.0001(13)
Troponin T, ng/l		20 (15-44)	15.5 (9.0-31.5)	14 (9-18)	8 (6-12)	0.0001(14)
C-reactive protein, mg/l		153 (86-219)	119 (59-198)	94.2 (40.5-148)	44.2 (20-89.7)	0.0001(15)
Albumin, g/l		24 (20-37)	27 (22-59)	27 (23-34)	31 (27-34)	0.004(16)
Interleukin 6, pg/ml		167 (44-968)	309 (42-1,113)	64 (27-496)	47 (23-183)	0.003(17)

Ferritin, ug/l		1271 (499-2653)	958 (423-2184)	1513.5 (817-2824)	775 (238-1484)	0.06
COMORBIDITIES						
Cardiovascular Diseases						
Cardiovascular disease*, n (%)		38 (60.3)	59 (66.3)	56 (56.6)	51 (32.9)	<0.0001[18]
Hypertension, n (%)		30 (47.6)	42 (47.2)	47 (47.5)	39 (25.2)	<0.0001[19]
Ischaemic heart disease, n (%)		8 (12.7)	14 (15.7)	11 (11.1)	8 (5.2)	0.05
Arrythmia, n (%)		8 (12.7)	16 (18.0)	9 (9.1)	14 (9.0)	0.16
Vasculopathy, n (%)		8 (12.7)	8 (9.0)	9 (9.1)	7 (4.5)	0.19
Valvulopathy, n (%)		2 (3.2)	5 (5.6)	3 (3.0)	4 (2.6)	0.67
Heart failure, n (%)		3 (4.8)	7 (7.9)	4 (4.0)	2 (1.3)	0.07
Other						
Diabetes mellitus, n (%)		9 (14.3)	21 (23.6)	20 (20.0)	18 (11.6)	0.07
Endocrinology disease, n (%)		7 (11.1)	17 (19.1)	13 (13.1)	18 (11.7)	0.37
Neurological disease, n (%)		8 (12.7)	16 (18.0)	13 (13.1)	12 (7.7)	0.12
Immune depression, n (%)		3 (4.8)	12 (13.5)	11 (11.1)	12 (7.7)	0.24
Hypothyroidism, n (%)		2 (3.2)	9 (10.1)	9 (9.1)	10 (6.5)	0.35
Kidney disease, n (%)		5 (7.9)	8 (9.0)	7 (7.1)	8 (5.2)	0.70
Orthopaedic disease, n (%)		3 (4.8)	7 (7.9)	8 (8.1)	13 (8.4)	0.86
Gastrointestinal disease, n (%)		6 (9.5)	8 (9.0)	4 (4.0)	10 (6.5)	0.42
Severe obesity, n (%)		6 (9.5)	12 (13.5)	1 (1.0)	7 (4.5)	0.002[20]
COPD, n (%)		7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04[21]
CKD, n (%)		3 (4.8)	9 (10.1)	5 (5.1)	6 (3.9)	0.26
BPH, n (%)		7 (11.1)	9 (10.1)	4 (4.0)	5 (3.2)	0.04[22]
Active solid cancer, n (%)		2 (3.2)	7 (7.9)	4 (4.0)	7 (4.5)	0.59
Previous cancer, n (%)		4 (6.4)	4 (4.5)	2 (2.0)	8 (5.2)	0.52
Stroke, n (%)		3 (4.8)	6 (6.7)	4 (4.0)	4 (2.6)	0.44
Other neurological disease, n (%)		4 (6.4)	5 (5.6)	4 (4.0)	1 (0.7)	0.03[23]
Asthma, n (%)		1 (1.6)	3 (3.4)	4 (4.0)	5 (3.2)	0.90
CHRONIC TREATMENTS						
ACEi at admission, n (%)		12 (19.1)	13 (14.6)	24 (24.2)	9 (5.8)	<0.0001[24]
ACEi name, n (%)	Ramipril	6 (50.0)	9 (64.3)	13 (54.2)	5 (55.6)	0.90
	Enalapril	2 (16.7)	3 (21.4)	8 (33.3)	3 (33.3)	0.71
	Lisinopril	1 (8.3)	1 (7.1)	1 (4.2)	0 (0.0)	-
	Perindopril	1 (8.3)	1 (7.1)	0 (0.0)	1 (11.1)	
	Zofenpril	1 (8.3)	0 (0.0)	1 (4.2)	0 (0.0)	
	Captopril	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	Zanipril	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	
ARBs, n (%)		9 (14.3)	16 (18.0)	10 (10.1)	26 (16.8)	0.41
ARB name, n (%)	Olmesartan	6 (66.7)	6 (35.3)	2 (20.0)	11 (40.7)	0.23
	Telmisartan	1 (11.1)	3 (17.7)	3 (30.0)	4 (14.8)	0.71
	Valsartan	1 (11.1)	4 (23.5)	1 (10.0)	5 (18.5)	0.84

	Irbesartan	0 (0.0)	3 (17.7)	3 (30.0)	4 (14.8)	-
	Losartan	1 (1.1)	1 (5.9)	1 (10.0)	3 (11.1)	
ACEi or ARBs, n (%)		21 (33.3)	29 (32.6)	34 (34.3)	34 (21.9)	0.10
IN-HOSPITAL TREATMENTS						
Lopinavir/ritonavir, n (%)		40 (63.5)	50 (56.2)	64 (64.6)	87 (56.1)	0.45
Hydroxychloroquine, n (%)		51 (81.0)	74 (83.2)	89 (89.9)	120 (77.4)	0.09
Corticosteroids, n (%)		26 (41.3)	37 (41.6)	24 (24.2)	18 (11.6)	<0.0001[25]
Tocilizumab, n (%)		17 (27.0)	21 (23.6)	27 (27.3)	22 (14.2)	0.03[26]
LMWH, n (%)		48 (76.2)	66 (74.2)	62 (62.6)	73 (47.1)	<0.0001[27]
Experimental drugs, n (%)		1 (1.6)	0 (0.0)	0 (0.0)	2 (1.3)	0.74
OUTCOMES						
CPAP during hospitalization, n (%)		45 (71.4)	50 (56.2)	49 (49.5)	32 (20.7)	<0.0001[28]
Median (IQR) CPAP max PEEP		12 (10-14)	10 (10.0-12.3)	10 (10.0-12.5)	10 (10.0-12.5)	0.02[29]
Intubation, n (%)		11 (17.5)	5 (5.6)	9 (9.1)	11 (7.1)	0.06
In-hospital mortality, n (%)		35 (55.6)	43 (48.3)	16 (16.2)	10 (6.5)	<0.0001[30]
Days from admission to death		15 (6-37)	25 (7-34)	35 (24-41)	36 (30-41)	0.0001[31]

*at least one of the following 6 categories

1. Severe VS Mild p-value= 0.02; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
2. Severe VS. Mild p-value= 0.04; Severe VS. Normal p-value= 0.005; Moderate VS. Normal p-value= 0.03.
3. Severe VS. Mild p-value= 0.0002; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value= 0.0007; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
4. Severe VS. Mild p-value= 0.04; Moderate VS. Mild p-value= 0.008.
5. Severe VS. Moderate p-value= 0.002; Severe VS. Mild p-value= 0.03; Moderate VS. Normal p-value= 0.0009; Mild VS. Normal p-value= 0.03.
6. Severe VS. Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value <0.0001; Moderate VS. Normal p-value <0.0001.
7. Severe VS. Moderate p-value= 0.04; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value 0.01; Mild VS. Normal p-value 0.001.
8. Severe VS Mild p-value= 0.03; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001.
9. Severe VS Mild p-value= 0.008; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value= 0.01; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.02.
10. Severe VS Mild p-value= 0.01; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value= 0.0006.
11. Severe VS Mild p-value= 0.002; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value= 0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0006.
12. Moderate VS. Normal p-value= 0.004.

13. Severe VS Mild p-value= 0.02; Severe VS Normal p-value <0.0001; Moderate VS: Mild p-value=0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.003.
14. Severe VS Normal p-value <0.0001; Moderate VS: Normal p-value=0.001; Mild VS. Normal p-value= 0.01.
15. Severe VS Mild p-value= 0.003; Severe VS Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0002.
16. Severe VS. Normal p-value= 0.002.
17. Severe VS. Normal p-value= 0.02; Moderate VS: Normal p-value=0.004.
18. Severe VS. Normal p-value= 0.0002; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.0002.
19. Severe VS. Normal p-value= 0.001; Moderate VS. Normal p-value= 0.0004; Mild VS. Normal p-value= 0.0003.
20. Severe VS. Moderate p-value= 0.009; Moderate VS. Mild p-value= 0.0007; Moderate VS. Normal p-value= 0.01; Mild VS. Normal p-value= 0.01.
21. Severe VS. Normal p-value= 0.02; Moderate VS. Normal p-value= 0.03.
22. Severe VS. Normal p-value= 0.02; Moderate VS. Normal p-value= 0.03.
23. NA
24. Severe VS. Normal p-value= 0.003; Moderate VS. Normal p-value= 0.02; Mild VS. Normal p-value <0.0001.
25. Severe VS Mild p-value= 0.02; Severe VS. Normal p-value <0.0001; Moderate VS Mild p-value= 0.01; Mild VS. Normal p-value= 0.008.
26. Severe VS. Normal p-value= 0.03; Mild VS. Normal p-value= 0.01.
27. Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value= 0.02; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
28. Severe VS. Mild p-value= 0.006; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value <0.0001.
29. Severe VS Moderate p-value= 0.005.
30. Severe VS. Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Mild p-value <0.0001; Moderate VS. Normal p-value <0.0001; Mild VS. Normal p-value= 0.01.
31. Severe VS Mild p-value <0.0001; Severe VS. Normal p-value <0.0001; Moderate VS. Normal p-value <0.0001.

Data are expressed as frequencies or medians (inter quartile range – IQR). Comorbidities with ≥3% prevalence were reported. A complete list of comorbidities is reported in Table 1 of the *Supplementary file*. ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; FEU: fibrinogen-equivalent

units; LMWH: low molecular weight heparin; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure.

The proportion of patients with cardiovascular comorbidities and hypertension was significantly higher in patients with a respiratory failure if compared with that of patients with a PaO2/FiO2 >300 mmHg (p-value <0.0001). Obesity was more prevalent in patients with moderate and severe respiratory failure if compared with obesity prevalence in patients with PaO2/FiO2 ≥201 mmHg (23% VS. 5.5%; p-value= 0.002); similar differences were found for COPD (22.2% VS. 7.2%; p-value= 0.04). Chronic use of ACEi was more prevalent in patients with respiratory failure (p-value <0.0001).

The highest proportion of intubated patients was in the severe group (17.5%) (Table 2).

Impact of cardiovascular diseases and RAA system inhibitors

Overall, chronic therapy with ACEi was associated with worse PaO2/FiO2 at admission (median value 223.5 VS. 273.0; p-value = 0.004) (Table 2 of the *Supplementary file*) and higher in-hospital mortality (35.6% VS. 23.5%; p-value = 0.048) (Table 2 of the *Supplementary file* and Figure 1). Severity of respiratory failure at admission, intubation and mortality rates were not associated with ARBs therapy (Table 3 of the *Supplementary file* and Figure 1).

Patients with CVD or hypertension had significantly lower PaO2/FiO2 at admission (both p-values <0.0001), a higher proportion of respiratory failure (both p-values <0.0001), and an increased need for CPAP during the hospital stay (p-value=0.02 and 0.003, respectively) (Table 4 of the *Supplementary file* and Table 3).

Table 3. Respiratory failure and outcomes in patients with cardiovascular disease, depending on ACEi and ARBs exposure.

	Covid-19 patients (n = 412)								
	CVD No (n= 205)	CVD yes (n= 207)	p-value						
				CVD yes (n= 207)					
				ACEi No (n= 154)	ACEi Yes (n= 53)	p-value	ARBs No (n= 147)	ARBs Yes (n= 60)	p-value
PaO2/FiO2 at admission	307.5 (180-381)	206.5 (123-305)	<0.0001	203 (127-319)	228 (113-290)	0.62	201.5 (118.0-285.5)	285.5 (135-343)	0.01
RF at admission, n (%)	125 (61.0)	174 (84.1)	<0.0001	129 (83.8)	45 (84.9)	0.85	128 (87.1)	46 (76.7)	0.06
CPAP at admission, n (%)	16 (7.8)	24 (11.6)	0.19	20 (13.0)	4 (7.6)	0.29	17 (11.6)	7 (11.7)	0.98
CPAP in-hospital, n (%)	76 (37.1)	100 (48.3)	0.02	75 (48.7)	25 (47.2)	0.85	71 (48.3)	29 (48.3)	1.00
In-hospital mortality, n (%)	32 (15.6)	72 (34.8)	<0.0001	53 (34.4)	19 (35.9)	0.85	58 (39.5)	14 (23.3)	0.03
Intubation, n (%)	23 (11.2)	13 (6.3)	0.08	9 (5.8)	4 (7.6)	0.74	9 (6.1)	4 (6.7)	1.00

Data are reported as frequencies or medians (interquartile range – IQR). CVD: cardiovascular disease; ACEi: angiotensin converting enzyme inhibitor; ARBs: angiotensin receptor blockers. PaO2: arterial partial pressure of oxygen; FiO2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

In hospital mortality and respiratory failure

In-hospital mortality was 25.5%. It proportionally increased with lower PaO2/FiO2 values, being highest in the severe group (55.6%) and lowest in patients with PaO2/FiO2 >300 mmHg (6.5%; p-value <0.0001). The number of days from admission to death was lowest in the severe group and highest in patients with normal PaO2/FiO2 at admission (p-value= 0.0001) (Table 2). Age > 65 years, male sex, exposure to ACEi, having a CVD, presence of respiratory failure at admission, a PaO2/FiO2 ≤ 200 mmHg, and need for CPAP at admission were significantly associated with an increased mortality at the univariate analysis (Table 4); however, the multivariate analysis showed that the only independent risk factors were age >65 years (Hazard rate (HR) 3.41; 95% confidence interval (CI): 2.00-5.78, p-value <0.0001), a PaO2/FiO2 ≤ 200 mmHg (HR 3.57; 95%CI: 2.20-5.77, p-value <0.0001) and the presence of respiratory failure at admission (HR 3.58; 95%CI: 1.05-12.18, p-value = 0.04) (Figure 2). Fifteen days post admission, patients with moderate to severe respiratory failure had a survival rate of 56% (Figure 2).

Table 4. Risk factors for in-hospital mortality.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >65 years	5.76 (3.46-9.60)	<0.0001	3.41 (2.00-5.78)	<0.0001
Males	1.58 (1.00-2.50)	0.049	1.17 (0.73-1.86)	0.52
Exposure to ACE inhibitors	1.68 (1.03-2.74)	0.04	1.28 (0.77-2.13)	0.34
Exposure to sartan	0.91 (0.52-1.61)	0.76		
Exposure to ACE inhibitors or sartan	1.33 (0.88-2.02)	0.17		
Cardiovascular disease	2.49 (1.63-3.79)	<0.0001	1.37 (0.88-2.13)	0.16
PaO2/FiO2 ≤200 mmHg	6.68 (4.25-10.52)	<0.0001	3.57 (2.20-5.77)	<0.0001
Presence of hARFat admission	15.08 (4.78-47.59)	<0.001	3.58 (1.05-12.18)	0.04
CPAP at admission	2.20 (1.32-3.67)	0.002	1.62 (0.96-2.72)	0.07

Multivariate Cox regression analysis that identifies risk factors for in-hospital mortality. Data are reported as hazard ratios (HR) and 95% confidence intervals (CI). ACEi: angiotensin converting enzyme inhibitor; PaO2: arterial partial pressure of oxygen; FiO2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

DISCUSSION

To the best of our knowledge, the results of the present study demonstrated for the first time the independent relationship between impaired gas exchange and clinical outcomes (mortality, intubation, and need for respiratory support).

We showed that age > 65 years, presence of respiratory failure and a PaO2/FiO2 ≤ 200 mmHg at admission were independently associated with a higher mortality rate. In fact, the mortality risk for patient without respiratory failure at admission was of 1% after 15 days from hospital admission. Conversely, survival in patients with a moderate to severe respiratory failure (PaO2/FiO2 ≤ 200 mmHg) at admission was only 56% at 15 days. The overall mortality rate in our cohort is comparable to previous reports.[5,24] However, it is higher if compared with the mortality described in other observational studies.[25,26] Richardson and coworkers reported a prevalence of respiratory failure (SpO2 <90%) of 20.4%,[25] whereas it was 72.6% in our cohort. Cheng et al. reported an in-hospital mortality as low as 11% in Wuhan, China. However, 58% of enrolled patients were not discharged from hospital at the time of the report,[26] whereas only 12% of our cohort was hospitalized at the time of writing.

Hypoxemia has been rarely considered as a risk factor for COVID-19 patients' outcome. Xie and colleagues showed that patients with SpO2 <90% had 47 times more the probability to die when compared with patients with SpO2 >90%.[27] However, in patients with COVID-19 associated pneumonia, low PaO2 values can be associated with satisfactory SpO2, hiding hypoxia, which might lead to an underestimation of the severity of the disease and in a treatment delay.[28] On this basis, clinicians should not rely solely on SpO2 values, especially when evaluating patients in which symptoms had lasted for 10-12 days before their presentation to the emergency department.[29] The ratio between PaO2 and FiO2 has been demonstrated to be a reliable tool to assess severity and stratify mortality risk.[17] When compared with the ARDS Berlin's definition, our respiratory failure classes had a slightly higher mortality with PaO2/FiO2 <200 mmHg (severe 55% VS. 45% and moderate 48% VS. 35%). This should probably depend on the cohort heterogeneity and in, in our case, the absence of 5 cmH2O of PEEP used in the Berlin definition to grade severity of ARDS. Another issue is the low number of patients with severe respiratory failure at admission who

underwent intubation (n= 11). This finding can be justified by the higher chance of DNI orders in patients with severe respiratory failure, secondary to the median age and to the higher prevalence of CVD.[5] However, the absence of respiratory failure at admission or a mild hypoxia did not preclude the chance of in-hospital death or intubation. Sign of respiratory distress and worsening gas exchange should be closely monitored, as a sudden and rapidly evolving disease can involve patients in stable conditions.[29, 30]

CVD and hypertension are the most frequently observed comorbidities in patients with COVID-19 and are associated with severe disease.[31, 32] A debate was focused on the negative effects of ACEi and ARBs due to the role of the ACE2 receptor in viral-host dynamics.[32] However, several studies ruled out the increased risk of COVID-19 infection and the link between disease severity and antihypertensive treatment.[28,31,33] Our cohort was characterized by a high prevalence of CVD (50.2%), which was associated with a significantly higher mortality compared with patients without CVD. However, mortality did not change in patients chronically exposed to ACEi and ARBs. ACEi was associated with a significantly higher mortality, potentially explained by the higher disease severity of at admission of patients taking ACEi. Indeed, neither CVD, nor hypertension, nor the exposure to antihypertensive medications were independently associated with decreased survival.

Study limitations

The initial gas exchange assessment was not homogeneously conducted in all patients at admission (only 30.3% of patients were in room air conditions). This might have underestimated the severity of respiratory failure, especially in patients treated with CPAP at admission. At the time of writing, 12% of patients were still hospitalized, biasing mortality and length of stay estimates. Furthermore, a selection bias could be hypothesized, being the participating centres hub for severe patients transferred from peripheral hospitals. The local standard operating procedures, criteria for ICU admittance or management with CPAP/NIV implemented in Italy could differ in other settings, limiting the inference of our findings.

CONCLUSIONS

The severity of respiratory failure assessed with the PaO2/FiO2 ratio is significantly associated with intubation rate, need for respiratory support, and in-hospital mortality. Age, respiratory failure and PaO2/FiO2 value at admission are independently associated with in-hospital mortality. Although the findings of the present study need to be confirmed in larger cohorts, they suggest that severity of hypoxemia can be useful to triage patients with COVID-19 pneumonia and identify patients at higher risk of unfavourable outcomes.

DATA AVAILABILITY

P.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the decision to submit for publication. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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COMPETING INTERESTS STATEMENT

The Authors have no competing interests to declare in regard with the present study.

AUTHORS' CONTRIBUTIONS

P.S. and D.R. conceived the study and contributed to data collection, analysis and interpretation. G.S. performed the data analysis and contributed to study design and interpretation. L.S. performed the analysis and contributed to data interpretation. P.M., C.C., G.D.F., M.R., E.F., S.P., F.G., M.D.M., G.N., V.V. AND F.T. contributed to data collection and interpretation. P.S., D. R., G.S. and L.S. drafted and revised the manuscript. All authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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The corresponding author here confirms that he has listed everyone who contributed significantly to the work.

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FIGURES' LEGENDS

Figure 1. Survival curves based on ACEi or ARBs exposure

Survival in patients hospitalized with COVID-19 pneumonia (n = 412) based on the chronic exposure to ACEi (angiotensin converting enzyme inhibitors, upper panel) or angiotensin receptor blockers (ARBs, lower panel).

Figure 2. Survival in patients hospitalized for COVID-19 based on age and severity of respiratory failure.

Hazard ratio for survival in patients hospitalized with COVID-19 pneumonia stratified by age (> or ≤ 65 years, Panel A), severity of respiratory failure at admission (PaO2/FiO2 ratio ≤ 200 mmHg and > 200 mmHg, Panel B) and presence of respiratory failure at admission (Panel C). Note that 15 days post admission, patients with moderate to severe respiratory failure had a survival rate of about 56%, while patients without respiratory failure (Panel C) had a survival rate of 99%.
PaO2/FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio.

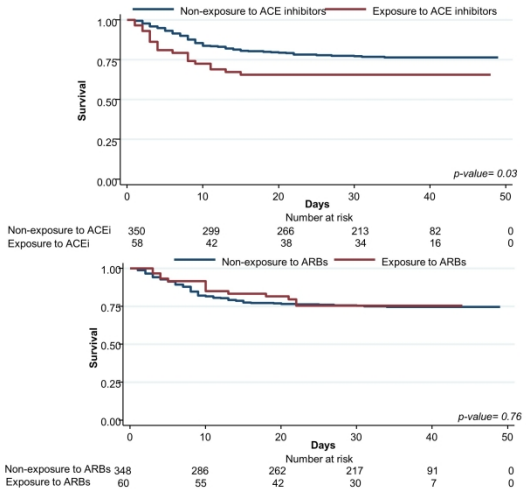

Figure 1. Survival curves based on ACEi or ARBs exposure
Survival in patients hospitalized with COVID-19 pneumonia (n = 412) based on the chronic exposure to ACEi (angiotensin converting enzyme inhibitors, upper panel) or angiotensin receptor blockers (ARBs, lower panel).

338x190mm (300 x 300 DPI)

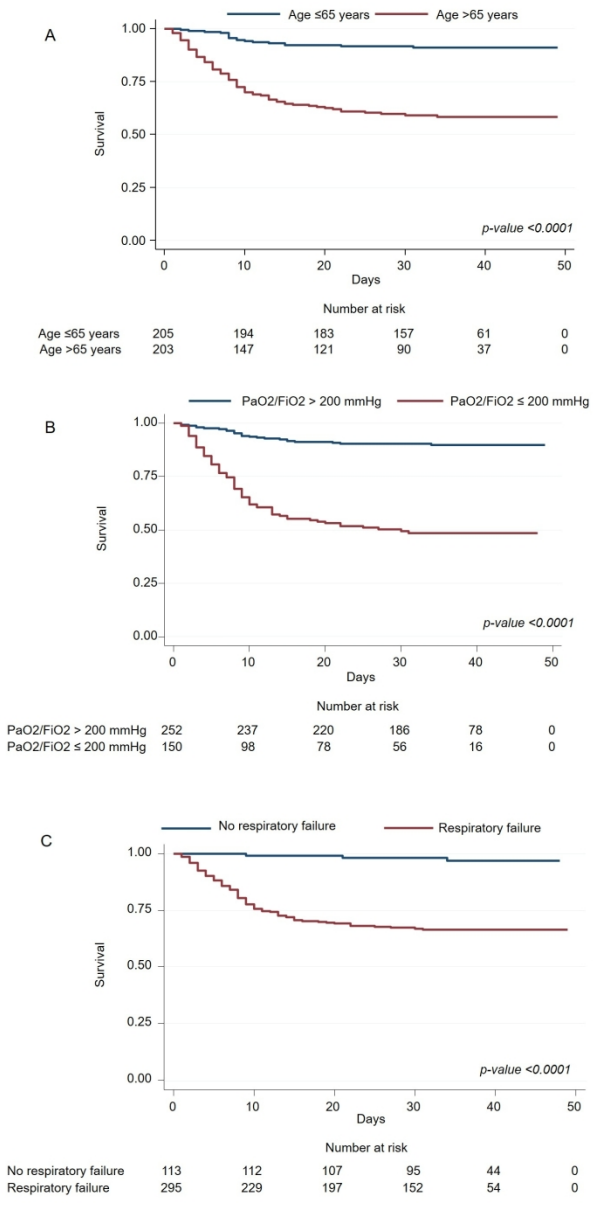

Figure 2. Survival in patients hospitalized for COVID-19 based on age and severity of respiratory failure. Hazard ratio for survival in patients hospitalized with COVID-19 pneumonia stratified by age (> or ≤ 65 years, Panel A), severity of respiratory failure at admission (PaO2/FiO2 ratio ≤ 200 mmHg and > 200 mmHg, Panel B) and presence of respiratory failure at admission (Panel C). Note that 15 days post admission, patients with moderate to severe respiratory failure had a survival rate of about 56%, while patients without respiratory failure (Panel C) had a survival rate of 99%. PaO2/FiO2: partial pressure of oxygen to fraction of inspired oxygen ratio.

232x466mm (150 x 150 DPI)

SUPPLEMENTAL MATERIAL

TITLE: SEVERITY OF RESPIRATORY FAILURE AT ADMISSION AND IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19: A PROSPECTIVE OBSERVATIONAL MULTICENTRE STUDY.

Participating centers

1. Division of Respiratory Diseases, Ospedale L. Sacco, ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy.
2. Department of Medicine and Rehabilitation, Division of Emergency Medicine, Ospedale Fatebenefratelli - ASST Fatebenefratelli-Sacco, Piazzale Principessa Clotilde, 3 - 20121 Milano, Italy.
3. Division of Internal Medicine, Ospedale L. Sacco - ASST Fatebenefratelli-Sacco, Via G.B. Grassi 74 – 20157, Milano, Italy.
4. Department of Health Bioscience, Università degli Studi di Milano—Respiratory Unit, Policlinico di San Donato, IRCCS— Via Rodolfo Morandi, 30 - 20097, San Donato Milanese, Milano, Italy.

The study protocol is available at: ClinicalTrials.gov: NCT04307459

Definition of immunocompromission

Immunocompromission was defined as the presence of ≥1 of the following risk factors:[1]

1. Acquired Immuno-Deficiency Syndrome (AIDS), defined either as human immunodeficiency virus infection with CD4+ lymphocyte count <200/μL or by the occurrence of AIDS-defining conditions;
2. aplastic anemia;
3. asplenia;
4. hematological cancer, defined as lymphoma, acute or chronic leukemia, or multiple myeloma;
5. chemotherapy during the last 3 months;

6. neutropenia, defined as a neutrophil count <500/dL at complete blood cell count;
7. biological drug use (including trastuzumab and therapies for autoimmune diseases, e.g., anti–tumor necrosis factor α, prescribed during ≥6 months before hospital admission);
8. lung transplantation;
9. chronic steroid use (>10 mg/d of prednisone or equivalent ≥3 months before hospital admission);
10. lung cancer with either neutropenia or chemotherapy;
11. other solid tumor with either neutropenia or chemotherapy;
12. other immunocompromise (any immunocompromised state, including congenital/genetic immunocompromised and immunosuppressive therapy due to hematological cancer/solid organ transplantation other than lung).

Criteria for hospitalization

Hospitalization criteria were based on the standard operating procedures created for the management of patients with suspected Covid-19,[2, 3] and on the latest international recommendations.[4, 5] Criteria included any of the following: 1) the presence of respiratory failure at admission (a PaO2 <60 mmHg while breathing room air or a PaO2/FiO2 ratio <300 mmHg); 2) age >65 years old with one or more comorbidities, pulmonary infiltrates at the chest X-ray or Ct scan and respiratory distress (a respiratory rate ≥ 30 breaths/minute and dyspnea); 3) pulmonary infiltrates and persistence of respiratory symptoms (cough, chest tightness, dyspnea at rest or during effort, fever) for more than 10 days; 4) pulmonary infiltrates with evidence of oxygen desaturation (drop in SpO2 of more than 4 units from resting value) while walking for 3 minutes; 5) hemodynamic instability, sepsis or shock; 6) sepsis and septic shock; 7) pulmonary infiltrates associated with confusion or a Glasgow Coma Scale <15; 8) inability to cope with outpatient therapy due to psychosocial or such as inability to maintain oral intake, history of substance abuse, cognitive impairment, severe comorbid illnesses, and impaired functional status.[5]

References

1. Di Pasquale MF, Sotgiu G, Gramegna A, et al; GLIMP Investigators. Prevalence and Etiology of Community-acquired Pneumonia in Immunocompromised Patients. *Clin Infect Dis* 2019;68:1482-93. doi: 10.1093/cid/ciy723.
2. Vitacca M, Nava S, Santus P, Harari S. Early consensus management for non-ICU ARF SARS-CoV-2 emergency in Italy: from ward to trenches. *Eur Respir J* 2020;2000632. doi: 10.1183/13993003.00632-2020.
3. Radovanovic D, Rizzi M, Pini S, et al. Helmet CPAP to Treat Acute Hypoxemic Respiratory Failure in Patients with COVID-19: A Management Strategy Proposal. *J Clin Med* 2020;9:E1191. doi: 10.3390/jcm9041191
4. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 13 March 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf. Accessed 17 May 2020.
5. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–67. doi: 10.1164/rccm.201908-1581ST.

Supplemental Table 1. Complete list of comorbidities observed in the study sample.

COMORBIDITIES	
Hypertension, n (%)	160 (38.8)
Ischaemic heart disease, n (%)	43 (10.4)
Arrythmia, n (%)	49 (11.9)
Vasculopathy, n (%)	32 (7.8)
Valvulopathy, n (%)	15 (3.6)
Heart failure, n (%)	17 (4.1)
Cardiovascular disease*, n (%)	207 (50.2)
Diabetes mellitus, n (%)	69 (16.8)
Severe obesity, n (%)	26 (6.3)
COPD, n (%)	25 (6.1)
Obstructive sleep apnoea syndrome, n (%)	5 (1.2)
Asthma, n (%)	13 (3.2)
Interstitial lung disease, n (%)	1 (0.2)
Active solid cancer, n (%)	20 (4.9)
Active haematological tumour, n (%)	7 (1.7)
Previous cancer, n (%)	18 (4.4)
Anaemia, n (%)	8 (1.9)
Immune depression, n (%)	39 (9.5)
Psychiatric disease, n (%)	12 (2.9)
Endocrinology disease, n (%)	57 (13.9)
Neurological disease, n (%)	49 (11.9)
Kidney disease, n (%)	31 (7.5)
Gastrointestinal disease, n (%)	28 (6.8)
MRGE, n (%)	12 (2.9)
Rheumatology, n (%)	4 (1.0)
Orthopaedic disease, n (%)	31 (7.5)
BPH, n (%)	25 (6.1)
Infectious, n (%)	7 (1.7)
Eye disease, n (%)	9 (2.2)
ORL, n (%)	4 (1.0)
Haematological disease, n (%)	8 (1.9)
Gynaecological disease, n (%)	9 (2.2)
Depression, n (%)	9 (2.2)
Others psychiatric disease, n (%)	5 (1.2)
Hypothyroidism, n (%)	32 (7.8)
Hyperuricemia, n (%)	4 (1.0)
Osteoporosis, n (%)	7 (1.7)
Others endocrinological disease, n (%)	8 (1.9)
Stroke, n (%)	17 (4.1)
Mental disability, n (%)	5 (1.2)
Alzheimer, n (%)	5 (1.2)
Dementia, n (%)	7 (1.7)

Epilepsy, n (%)	8 (1.9)
Others neurological disease, n (%)	14 (3.4)
CKD, n (%)	25 (6.1)
Kidney stones, n (%)	7 (1.7)
Others renal disease, n (%)	7 (1.7)
Cholecystectomy, n (%)	9 (2.2)
Appendectomy, n (%)	9 (2.2)
Gastric/Duodenal ulcer, n (%)	6 (1.5)
Chronic Hepatitis-C, n (%)	6 (1.5)
Others gastro, n (%)	18 (4.4)
Prosthetics, n (%)	12 (2.9)
Hernia, n (%)	14 (3.4)
Others surgery, n (%)	8 (1.9)
Hysterectomy, n (%)	7 (1.7)
Others gynaecology, n (%)	0 (0.0)

BPH: benign prostate hypertrophy; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CPAP: continuous positive airway pressure; LMWH: low molecular weight heparin; ORL: otolaryngology.

Supplemental Table 2. Respiratory failure and outcomes in patients exposed and not exposed to angiotensin converting enzyme inhibitors

	Not-exposure to ACE inhibitors (n= 353)	Exposure to ACE inhibitors (n= 59)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	273 (148.0-346.5)	223.5 (113-290)	0.004
Presence of respiratory failure at admission, n (%)	250 (70.8)	49 (83.1)	0.05
Need for CPAP at admission, n (%)	34 (9.6)	6 (10.2)	0.90
Need for CPAP during the hospital stay, n (%)	148 (41.9)	28 (47.5)	0.43
In-hospital mortality, n (%)	83 (23.5)	21 (35.6)	0.048
Need for intubation, n (%)	31 (8.8)	5 (8.5)	0.94

ACEi: angiotensin converting enzyme inhibitors; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 3. Respiratory failure severity and outcomes in patients exposed and not exposed to angiotensin receptor blockers

	Non-exposure to ARBs (n = 351)	Exposure to ARBs (n= 61)	p-value
Median (IQR) PaO_2/FiO_2 ratio at admission, mmHg	262 (140-341)	289 (140-343)	0.98
Presence of respiratory failure at admission, n (%)	252 (71.8)	47 (77.1)	0.40
Need for CPAP at admission, n (%)	32 (9.1)	8 (13.1)	0.33
Need for CPAP during the hospital stay, n (%)	146 (41.6)	30 (49.2)	0.27
In-hospital mortality, n (%)	90 (25.6)	14 (23.0)	0.66
Need for intubation, n (%)	32 (9.1)	4 (6.6)	0.63

ARBs: angiotensin receptor blockers; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

Supplemental table 4. Severity of respiratory failure and outcomes in patients with hypertension compared with patients without hypertension.

	Hypertension (n = 160)	No-hypertension (n= 252)	p-value	No-hypertension (n= 252)			
				Without CVD (n=205)	p-value*	With CVD (n= 47)	p-value*
PaO_2/FiO_2 at admission, mmHg	214.5 (120.0-300.0)	291.5 (153.5-362.0)	<0.0001	307.5 (180-381)	<0.0001	184 (126-310)	0.65
Respiratory failure at admission, n (%)	135 (84.4)	164 (65.1)	<0.0001	125 (61.0)	<0.0001	39 (83.0)	0.82
CPAP at admission, n (%)	18 (11.3)	22 (8.7)	0.40	16 (7.8)	0.26	6 (18.8)	0.78
CPAP in-hospital, n (%)	76 (47.5)	100 (39.7)	0.12	76 (37.1)	0.045	24 (51.2)	0.67
In-hospital mortality, n (%)	53 (33.1)	51 (20.2)	0.003	32 (15.6)	<0.0001	19 (40.4)	0.36
Intubation, n (%)	10 (6.3)	26 (10.3)	0.15	23 (11.2)	0.10	3 (6.4)	0.97

A sensitivity analysis has been performed excluding patients with cardiovascular diseases from patients without hypertension. PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inhaled oxygen; CPAP: continuous positive airway pressure.

* VS. patients with hypertension

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract DONE – page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. DONE – page 3 and 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. DONE – page 6
Objectives	3	State specific objectives, including any prespecified hypotheses. DONE – page 6
Methods		
Study design	4	Present key elements of study design early in the paper. DONE – page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. DONE- page 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. DONE- page 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed. N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. DONE - page 7 and 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. DONE – page 7 and 8
Bias	9	Describe any efforts to address potential sources of bias. DONE – page 7 and 8
Study size	10	Explain how the study size was arrived at DONE - page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. DONE page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. DONE – page 9
		(*b*) Describe any methods used to examine subgroups and interactions. DONE – page 9
		(*c*) Explain how missing data were addressed. DONE, table 1 (pages 10-12)
		(*d*) If applicable, explain how loss to follow-up was addressed. N/A
		(*e*) Describe any sensitivity analyses. N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. DONE – Page 9
		(b) Give reasons for non-participation at each stage. N/A
		(c) Consider use of a flow diagram. N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. DONE - page 10-12
		(b) Indicate number of participants with missing data for each variable of interest - DONE - page 10-12
		(c) Summarise follow-up time (eg, average and total amount). DONE – page 16-16
Outcome data	15*	Report numbers of outcome events or summary measures over time. DONE – page 15-16 and Figure 1

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. DONE – page 20
		(*b*) Report category boundaries when continuous variables were categorized. DONE – page 20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. DONE – Page 18 and Supplementary material Tables 2 to 4
Discussion		
Key results	18	Summarise key results with reference to study objectives. DONE – Page 21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. DONE – Page 22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. DONE – Page 21-22
Generalisability	21	Discuss the generalisability (external validity) of the study results. DONE – Page 22
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. DONE – Page 23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.